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THE PAEDIATRIC APPROACH TO TONSILLECTOMY*

BY

J. ALISON GLOVER, C.B.E., M.D., F.R.C.P., D.P.H.

Tonsillectomy is by far the most frequent operation done under a general anaesthetic, and in the last twenty years far more than one and a half million tonsillectomies have been done on public elementary school children in England and Wales. It is an operation not devoid of risks or even of mortality and, as the Journal of the American Medical Association (Editorial, 1947) (a journal by no means prejudiced against it) has recently stated, it 'should command all the respect of a major operation.' Its incidence, despite much criticism of mass tonsillectomy, is still excessive.

Incidence

The eccentricities of the incidence of tonsillectomy distinguish it from that of any other surgical procedure or morbid condition. In this country its frequency has mounted in some forty-five or fifty years from almost none to some two hundred thousand a year, and in the children of the well-to-do it is more than three times as high as in children who attend public elementary schools.

Local Incidence

If this latter, the incidence upon public elementary school children, be studied from the official returns made by local authorities of tonsillectomies done under their schemes of treatment, comparisons between neighbouring or similar areas often show startling differences in the tonsillectomy rates, that is, in the number done each year shown as a percentage of the children in average attendance at the public elementary schools in that area. These great variations in local incidence are unrelated to any climatic, environmental, or nutritional factor, but appear to depend almost entirely upon medical opinion in the individual area. The table shows the incidence in Kent in the last three pre-war years. The rate in these three years was relatively constant in each area. The unimpressive looking percentages for England and Wales given for comparison represented the enormous numbers of about 81,000, 84,000 and 89,000 tonsillectomies done in the respective years.

Kent County Council, comprising largely rural areas, had for the three years exactly the same average percentage rate as England and Wales, and the actual number of operations done in 1938 was 1,362.

Of the urban areas in Kent, seven—Beckenham, Chatham, Dover, Maidstone, Rochester, Erith, and Penge—had practically the same rate as the county and England and Wales (1·8 per cent.). Faversham (1·3) and Gravesend (1·2) had somewhat lower rates, and Ramsgate (0·9) had just half the national rate. In Deal hardly any were done under the local authority's scheme. Deal, in this respect, had good companions in other counties. But Canterbury (3·5), Bromley (3·5) and Folkestone (3·9) had twice—and Bexhill (5·0) and Royal Tunbridge Wells (4·7) nearly three—times the county and national rate. Column 3 shows what these rates meant when applied to the nine years of a child's elementary school life. A child in a Bexhill elementary school was five times more likely to have his tonsils out than was a child in Ramsgate, and, by the time elementary school life was over, nearly 50 per cent. of Bexhill children would have been tonsillectomized. Margate had a rate three and a half times that of Ramsgate, and Royal Tunbridge Wells one nearly three times that of Beckenham. Elsewhere (Glover, 1938) I have given still more striking contrasts in other counties.

TABLE

KENT EDUCATION AREAS: ANNUAL PERCENTAGE RATE OF ALL CHILDREN IN 'AVERAGE ATTENDANCE' AT PUBLIC ELEMENTARY SCHOOLS TONSILLECTOMIZED IN THE LAST THREE PRE-WAR YEARS

Education Authority	1			2	3
	Annual tonsillectomy rate			3-years average	Percentage of children who would be tonsillectomized during the nine years of school life (i.e. (2) × 9)
	1936	1937	1938		
E. and Wales	1·7	1·8	2·0	1·8	16
Kent C.C. ..	1·9	0·9	2·6	1·8	16
Canterbury C.B.	2·7	3·6	4·1	3·5	32
Beckenham ..	1·4	1·8	2·3	1·8	16
Bexhill ..	5·5	4·3	5·5	5·0	45
Bromley ..	3·3	3·5	3·8	3·5	32
Chatham ..	1·4	1·8	2·0	1·7	15
Deal ..	0·2	0	0	0·1	1
Dover ..	1·4	1·7	2·1	1·7	15
Faversham ..	1·4	1·4	1·2	1·3	12
Folkestone ..	3·9	4·4	3·5	3·9	35
Gillingham ..	2·4	2·5	2·8	2·6	23
Gravesend ..	0·6	0·9	2·2	1·2	11
Maidstone ..	1·0	2·0	1·6	1·9	17
Margate ..	2·5	2·7	3·7	3·0	27
Ramsgate ..	0·5	0·9	1·4	0·9	8
Rochester ..	1·7	2·3	1·5	1·8	16
R. Tunbridge W.	4·0	6·2	3·9	4·7	42
Erith ..	1·4	2·8	2·4	2·2	20
Penge ..	1·9	1·8	2·3	2·0	18

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* Presidential address to the Kent Paediatric Society, 1947.

Social Incidence

But these elementary school percentages in column 3, of children who have been tonsillectomized by the end of their school life at fourteen years, look small beside those of the pupils of wealthy public boarding schools, who have been tonsillectomized before entry at about thirteen and a half years.

The Report of the Schools Epidemic Committee, dealing with seventeen large boarding schools for boys and nine large public boarding schools for girls shows that in 1934 58·2 per cent. of boys and 50·1 per cent. of girls were tonsillectomized, and that these percentages had risen by 6·0 per cent. and 7·0 per cent. in five years, although in the same years the number of tonsillectomies done in the public elementary schools had shown a reduction of one-third, this being in response to the strong criticism of excessive operating which culminated in 1931. Most public school pupils had been operated upon before entry. At Eton in 1938 some 83 per cent. of new boys were found to have been tonsillectomized before entry. In general, the wealthier and the more exclusive the school the higher is the tonsillectomy rate, and for a boy ‘ to be born with a silver spoon in his mouth ’ seems to be one of the conditions which lead to tonsillectomy.

Sex Incidence

Boys are more frequently tonsillectomized than girls, and earlier in life, though girls seem to suffer as much from acute tonsillitis as boys. Maternal solicitude may be a factor, for the boy of five to seven years more often looks skinny and miserable than the girl.

The Age Incidence

A consideration of age distribution of incidence is of great importance in our paediatric approach. The highest incidence* occurs between five and seven years with the peak at six, and thus coincides with the end of the second ‘ springing up ’ phase of the child’s development, and with great changes in his dentition and in his environment, for he then first comes into contact with the fresh infections of school life. If the tonsil has a function ‘ absorbing small numbers of organisms and so establishing immunity by gradual dosage ’ (Griffith, 1937) this is the time when it is most likely to be useful, and when enlargement might be expected and might even be beneficial. In fact the fate of many a tonsil seems like that of the poor faithful hound Gelert, whose abnormal appearance caused his death before they found the dead wolf he had slain and the unhurt child he had saved.

Many of the operations performed at this age of rapid development remove tonsils which have become enlarged in response to their protective function. Some of the improvement ascribed in these cases to tonsillectomy may well be due to developmental changes which take place at this stage in the child’s life, the critical age of seven according to Hippocrates, and according to Harris (1931) the year of transition from the second ‘ springing up ’ period to the second ‘ filling out ’ period of eight to ten years.

Neuber (1932) in Hungary found that in the lower forms of elementary schools children with ‘ hypertrophic ’ tonsils had a greater average height and weight than those with ‘ normal ’ tonsils.

Ellis and Russell (1937) wrote of the 4,000 Basque children who had come out of siege conditions and terrible overcrowding to Southampton: ‘ Another revealing feature of the group was the appearance of the children’s throats. Less than 2 per cent. had had tonsillectomies performed, and in a very great number of cases the tonsils were as large or larger than walnuts. But the incidence of both cervical adenitis and otorrhoea was only approximately 0·4 per cent., and that of obvious respiratory infection almost incredibly low. The same is true of nasal discharges and respiratory obstruction.’

Epstein (1937) has shown that even in carefully selected cases better results were obtained by tonsillectomy in children between six and ten years, than in children under six.

Indications for Tonsillectomy

Though as Dean (1934) has said, ‘ it is always a gamble,’ few will deny that in a properly selected case tonsillectomy may have brilliant results. Why has this useful operation been debased into ‘ so widespread an attack upon a normal structure of the body ’ (Paton, 1928) ? Why have its probable function in childhood and its tendency to spontaneous involution alike been so often overlooked in this wholesale and hasty resort to symptomatic treatment in its crudest form ? These questions form the crux of my subject.

The indications for operation fall into two main groups: the ‘ objective ’ (size and appearance), and the ‘ indirect,’ the hoped-for prophylactic or curative effect of the removal of the tonsils on respiratory infections and other conditions.

Objective Indications

As regards the first group they are almost invariably present, that is, the tonsils either are large, or look ‘ diseased ’ or ‘ infected ’ or ‘ pathological.’

Nowadays fortunately it is generally said that the size of the tonsil (which after all may be only the sign of hard immunological duty well done) is of no clinical importance unless there is real obstruction, which is a rare condition. ‘ If the standard of size be adopted many innocent tonsils will be sacrificed whilst some of the worst offenders will escape ’ (Allen, 1932). But though this be said I fear many a tonsil is still condemned on size alone, for slight enlargement without any other symptom was the only indication in 31 per cent. of Griffith's (1937) series of 4,500 children sent to hospital for tonsillectomy. Most books state that obviously 'diseased' or 'pathological' or 'infected' tonsils should be removed. Some think these conditions can be ascertained by inspection, and consider a band of chronic dark red congestion in the mucous membrane covering the anterior fauces diagnostic. Others, like Scott Stevenson (1935) and Ballenger (1943) consider the presence of pus in the crypts, shown by pressing the anterior pillar when muco-pus or cheesy matter exudes from some of the crypts, a most important sign. Even here we have much contradiction. Epstein (1937) found large tonsils almost always infected and that redness of the anterior pillars was not a reliable indication of infection. Others say that abscessed crypts are practically always found after infancy. Epstein found no evident connexion between the amount of caseous matter in the crypts or the size of the crypts and the results of removal. But Dean (1934) writes that 'he could not identify a chronically diseased tonsil except after removal and microscopic study,' which recalls the old Guy's aphorism, 'Call no man healthy until he is dead and Dr. Moxon has performed the post-mortem.' Epstein, by no means a disbeliever in sane tonsillectomy, goes further: 'There are two objections to the dictum that an infected tonsil should come out. The first is that it usually has no bearing on the situation in children, whose tonsils are removed usually because of infections of the upper respiratory tract. The second objection is that even if infected tonsils ought to be removed, the dictum is valueless because the physician admittedly does not know an infected tonsil when he sees one. As pointed out previously there is not even agreement as to the diagnosis of infection on microscopic examination, let alone on clinical examination . . . there is nothing to lead one to feel that the appearance of the tonsils should ever influence one's judgment as to the advisability of removing them for the improvement of the child's health.'

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* Rolleston (1939), in 870 children found the highest incidence between 4 and 6 years with a sharp peak at 5 years.

It is obvious that an organ of which the probable purpose is to arrest invading organisms must be 'infected.'

The *Lancet* recently (Editorial, 1943) said, 'It now seems probable that the tonsil by trapping pathogenic bacteria, not only may act as a front line guard against infection, but may also contribute to the production of antibodies specific against the invading micro-organisms. Enlargement of lymph glands in response to infection is commonplace, and is not as a rule accompanied by increase in blood lymphocytes. Rantz studied specific antibodies in sixty-four children who were streptococcal throat carriers, thirty-three of whom were proved by culture of the excised tonsil to have been carriers of Group A haemolytic streptococci. He found a quick and consistent fall of antistreptolysin and correlated the reduction in circulating antibody with the removal of the antigenic stimulus in the tonsil. The argument seems to be in favour of a conservative attitude towards the enlarged tonsil.'

Indirect Indications

Many textbooks and papers give us lists of indirect indications, sometimes with percentage frequencies. Here is one by Ash (1931) of the indications in nearly 1,700 cases in elementary school children, gathered into twelve groups: 20 per cent. for frequent sore throats and tonsillitis; 12 per cent. for frequent colds; 12 per cent. for chest conditions; 11 per cent. for enlarged turbinates and deviated nasal septum; 11 per cent. for earache and obstructive deafness; 4 per cent. tubal catarrh; 6 per cent. otitis media; 6 per cent. enlarged cervical glands; 4 per cent. rheumatic conditions; 9 per cent. 'systemic and general conditions'; 3 per cent. eye conditions; 4 per cent. 'reflex conditions.' Another authority gave thirty-three indications (in seven groups) and a recent text book forty-seven. The length of and great variation in such lists suggest that many of the indications shown in them may be of little value, and recalls the words of Sanford Blum who, as early as 1915, wrote, 'Tonsillectomy has become a menace. It is performed not only where definite indications are present, but also for the most trifling reasons (witness reports of reputable physicians that they consider anorexia, faucial hyperemia, restless nights, indications for tonsillectomy) and sometimes for no reason.'

Acute tonsillitis. It is generally agreed that frequently repeated attacks of acute tonsillitis form the most reliable indication. It is the one assigned in about one-fifth to one-third of the cases in most series. But how frequent have the repetitions to be to condemn the tonsil? Acute tonsillitis may be a reaction to invasion by S. pyogenes and protective rather than dangerous.

Layton (1938) suggested three acute attacks within one year, or two if accompanied by joint pains. Most authorities merely say 'repeated' or 'frequent.' As the frequency of sore throats decreases rapidly as age increases, this indication must be related to the age of the patient. An attack sustained during an epidemic of sore throats, scarlet fever, influenza, or measles, in the community of which the child is a member, should be regarded as a protective reaction.

The possibility of a child having repeated attacks of acute tonsillitis because some intimate contact is a carrier of S. pyogenes should be borne in mind.

Recurrent quinsy is a strong indication for tonsillectomy after an appropriate interval, but quinsy rarely occurs in children.

Frequent colds. Frequent colds, nasal catarrhs, and coughs are still often invoked to justify operation. Epstein, who had 'fair results' in older children, found results for head colds and coughs 'especially poor' in those under six years, and particularly so in those under four. Bradley (1930) in England, like Smiley (1924) and Forsythe (1928) in America, thought little of this indication. More recently Griffiths (1937) has written, 'In no circumstances should tonsils be removed for nasal catarrh.' Layton (1938) ' did not believe recurring colds were ever cured by tonsillectomy,' and Rodgers (1940), 'Tonsillectomy done for colds in the head was needless and sometimes harmful.' Paton (1943), judging by school days lost in a well-to-do boarding school observed over ten years, found that 435 tonsillectomized girls ' suffered much more from respiratory infections ' than 393 non-tonsillectomized girls.

Thus, although thousands of tonsillectomies are still done to prevent colds, nasal catarrhs, and coughs, opinion now tends to regard them rather as symptoms of sinusitis, than as indications for tonsillectomy, which is neither preventive nor curative of them.

Sinusitis. Sinusitis, long considered to be an indication for tonsillectomy, is now regarded rather as a cause of tonsillitis. Griffith found that first attacks of sinusitis occurred more commonly in his operated children, and Kaiser (1942) that tonsillectomy rarely benefits this condition. Crookes (1938) concludes first that ' disease of the tonsils and adenoids is not a common cause of sinusitis and that their removal is neither a preventive nor a cure of the condition . . . sinusitis is a common cause of inflammation of the adenoids and to a lesser degree of the tonsils. The first step in the treatment of sinusitis is the treatment of the sinus itself and not the removal of the tonsils and adenoids.'

Birdsall (1939) writes, 'Tonsillectomy is often performed upon children with sinusitis without any beneficial results. Careful examination of the nose would prevent this error in a large proportion of cases.'

Bronchitis. Even recent textbooks, like that of Hall (1941), give ' bronchitis and other chest conditions associated with colds and sore throats ' as indications. Twelve per cent. of Ash's children and 14 per cent. in Griffith's series had been operated on for 'chest conditions.' The general trend of opinion now is, however, towards regarding bronchitis and pneumonia rather as contra-indications.

Kaiser found that bronchitis occurred ' somewhat more frequently ' and pneumonia ' more frequently ' in the tonsillectomized children than in the unoperated controls of his series (who are particularly valuable as controls because they had initially been considered just as suitable for tonsillectomy, but for some reason had not had the operation).

The value of deductions from statistics such as those of Paton or of the School Epidemics Committee from boarding schools with high proportions of their pupils tonsillectomized is somewhat lessened by the argument that although the tonsillectomized may suffer more from colds and chest conditions than the non-tonsillectomized, they might have suffered still more than they did, and, further, that the operation rendered them nearly as resistant as their non-operated companions. But this latter argument seems to lose much of its force when a very high proportion of the pupils, such as obtains in some wealthy schools, is tonsillectomized.

Asthma and allergic conditions. Denzer and Felshin (1943) found that, in 11 per cent. of 217 children presented for tonsillectomy, asthma or some other allergic condition unlikely to be relieved by operation was the cause of the symptoms. Tonsillectomy has no beneficial effect on asthma, allergic conditions, or toxic acidosis.

Enlarged cervical glands. These accounted for 6 per cent. in Ash's series, and 15 per cent. in Griffith's and are rated high by the textbooks. Hall specifies ' prolonged glandular enlargement which does not subside with the recovery of the tonsillar infection '; Lederer (1943) ' recurrent or persistent '; Denzer ' when it occurs in children with large or diseased tonsils with frequent upper or lower respiratory disease.' In Kaiser's series 15 per cent. alike of operated and control groups had visible enlargement; he found that, for this condition, tonsillectomy was justified and the benefit striking. Paton, on the other hand, found adenitis more common in those girls whose tonsils had been removed. Davis (1938) found cervical adenitis was common and more severe in tonsillectomized patients. Hobson (1938) regards a persistent though varying enlargement associated with tenderness on pressure and recurrent febriculae as important clinical evidence of chronic tonsillar infection and, in the absence of sinusitis and dental sepsis, an indication for tonsillectomy ; but he nevertheless finds enlargement as obvious and universal in the tonsillectomized as in those with intact tonsils, and that an acute adenitis in the tonsillectomized individual is a peculiarly noticeable feature of many streptococcal epidemics.

Otitis media. Lederer places this indication high (fourth) on his list, as does Hall. It was the indication in 6 per cent. of Ash's series, in addition to 11 per cent. for ' earache ' and ' obstructive deafness,' and 4 per cent. for ' tubal catarrh,' that is, 21 per cent. in all for ear conditions. ' Ear conditions ' were the indication in 3·4 per cent. of Paterson's series, and ' deafness ' for 4 per cent. in Griffith's.

In Kaiser's series purulent otitis media had occurred before operation in 15 per cent. of the operated children and 12 per cent. of the non-operated controls. After ten years' follow-up he thinks less of this indication than after three years. During the three years following the operation the incidence was considerably lower in the operated than in the controlled, but during the next seven years the controls fared somewhat better than the operated.

Davis writes, 'Symmetrical (i.e. of both ears) catarrhal otitis media, when not due to any other cause, makes tonsillectomy and the removal of adenoids imperative.' Griffith concludes that tonsillectomy does not necessarily improve cases of middle-ear disease. Tumarkin (1937) pronounces strongly against this indication.

The Epidemics in Schools Committee found some slight indication that the incidence of rheumatism, otitis media, and mastoid disease is higher in the tonsillectomized, but here again pointed out that it might have been higher in them if tonsillectomy had not been performed.

There is evidence that drastic reduction in the number of tonsillectomies by no means increases the incidence of otitis media and cervical adenitis. The Derbyshire school medical service (Glover, 1938) in the three year period 1929-31 did on an average 2,394 tonsillectomies a year, and found at routine and special examinations an average of 243 cases of otitis media and 872 of enlarged cervical glands. Drastic reduction in tonsillectomy begun by Ash in 1932, and three years later, in the three-year period 1935-37, the yearly average of tonsillectomies done was 178, less than one-thirteenth of the average in 1929-31; the average number of cases of otitis media found was reduced to 192 and of enlarged cervical glands to 632.

Similar reductions in the case of otitis media followed even more drastic reductions of tonsillectomies by Garrow in Hornsey, which began in 1929 (Glover, 1938).

Tonsillectomy is in some cases the cause of suppurative otitis media. Keen (1932), in 9,344 tonsillectomies, found that sixty (0·64 per cent.) of children who had not had otitis previously, besides seven others in whom a previous otitis recurred, developed suppurative otitis media directly following the operation. The sixty included six with mastoiditis and intracranial complications of which three children died. Burton and Sandiford report that at the Ilford Aural Clinic (1939) of 212 cases of otorrhoea seen in four years, the original cause of the primary otitis media in seventeen cases (8 per cent.), was tonsillectomy.

O'Donnell had five (0·85 per cent.) cases of acute otitis media following 588 tonsillectomies, and Nesbitt (1934) twenty-two (1·5 per cent.) in 1,459 out-patient children at the Royal Infirmary, Edinburgh.

Nephritis. Nephritis, though not numerically important as an indication, is of interest as an example of how hard it is to get rid of a fallacious indication. It is a well defined condition for which tonsillectomy was confidently recommended, and still is by some. It has been studied by Illingworth (1939) at Great Ormond Street, where no bias against the operation could be suspected, for over eleven years. He shows that (a) tonsillectomy does not prevent nephritis, but may predispose to it, (b) tonsillectomy does not cure nephritis or prevent it from progressing to the chronic stage, (c) tonsillectomy may cause nephritis.

Nevertheless six months after the publication of Illingworth's paper, a distinguished surgeon on the staff of the same hospital, writing that nephritis is another disease which in many cases is secondary to tonsillitis (which is of course true), goes on to say, 'Although grave damage has already been done further injury can be arrested by timely attention to the source of infection' (that is, tonsillectomy).

How slow medical opinion is to abandon tonsillectomy as a remedy is shown by its being done in the acute stage in 119 cases though no beneficial effect on the urinary condition was observed in any case. In 5 per cent. of the three hundred cases tonsillectomy was the probable cause of the nephritis. There seems little doubt that nephritis should be transferred from 'indication' to 'contra-indication.'

Acute rheumatism and carditis. Gradually medical opinion has turned against this indication in which twenty years ago I believed. Some, while recognizing that the operation is neither a preventive nor a cure of rheumatic disease or of its recurrence, still hesitate to relinquish it. Wallace and Brownlie-Smith (1936) found no evidence that tonsillectomy before the age of five years protects a child against acute rheumatic infection, and that comparison with a controlled series of cases suggests that tonsillectomy during early childhood may even increase a child's susceptibility to acute rheumatism.

Summary

As paediatricians our approach to tonsillectomy should be cautious and should take into account the following considerations,

1. Despite criticism, the incidence of tonsillectomy, the most frequent cause of hospital admission, remains excessive, particularly in children between five and seven years of age.

2. This age distribution suggests that many tonsillectomies are done because of enlargements which are either physiological, associated with the great changes in development during this critical period, or immunological responses to the unaccustomed infections met with on entry to school, or to the sepsis resulting from the decay of the primary teeth.

3. Tonsils cannot be determined as 'diseased' or 'infected' by clinical examination; as their function includes the arrest of pathogenic organisms, the fact that these can be found in them after removal forms no justification for the operation.

4. Tonsillectomy should command all the respect due to a major operation. In a proportion of cases it is followed by unpleasant sequelae, and it has a mortality which, though small, is larger than is generally appreciated. Moreover, tonsillar remnants are often left, which may be more harmful than the original tonsils.

5. The most reliable indication is the occurrence of frequently repeated attacks of acute tonsillitis

which cannot be explained by extraneous infection.

6. Some indications still often held to justify the operation, particularly frequent colds, chronic nasal catarrh, and otitis media are misleading. To remove the tonsils to cure sinusitis is to put the cart before the horse. Certain other conditions, including bronchitis, asthma, and nephritis, are definitely contra-indications. The value of the operation in benefiting acute rheumatism is doubtful.

7. The operation has no value as a prophylactic against common infectious diseases, with the possible exception of diphtheria. In residential schools with high tonsillectomy rates, while the incidence of recurrent sore throats may be somewhat diminished, that of frequent colds is slightly increased. The incidence of otitis and mastoid disease is the same, or perhaps slightly increased, in the tonsillectomized, while their liability to bronchitis and pneumonia is also increased.

8. The operation is never urgent, and should always be preceded by a period of observation of six months after the completion of any necessary treatment of teeth or sinuses. It should not be done in winter or early spring, or during the prevalence of infectious diseases, especially of measles or influenza, and most of all when poliomyelitis is epidemic.

9. Further critical and controlled investigation of the indications for and after-results of tonsillectomy are needed, with further study of the optimum age; probably these could best be carried out at the type of clinic resembling the 'Upper Respiratory Clinic for Children' suggested by Mr. Capps, or the pre-tonsillectomy clinic at Mount Sinai Hospital described by Denzer.

10. It is well to remind ourselves that in 1885 that great paediatrician, Goodhart, said of tonsillar enlargement, 'It is comparatively seldom that an operation is necessary . . . children generally grow out of it and at fourteen or fifteen years of age the condition ceases to be a disease of any importance.'

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FURTHER OBSERVATIONS ON THE SIGNIFICANCE OF THE BLOOD PYRUVIC ACID LEVEL IN INFANCY*

BY

E. C. ALLIBONE, M.D.

(From the Children's Hospital, Birmingham)

In a previous paper it was shown (Allibone and Finch, 1946) that toxic and infective states raised the blood pyruvic acid level in spite of what normally would have been an adequate thiamine intake. This phenomenon was particularly noticeable in infancy. Two factors had now to be considered. The first was whether the vitamin was being absorbed. Diarrhoea, which obviously would interfere with absorption, is particularly common in toxic states in infancy. In the group of infants observed above, diarrhoea, though frequent, was not an invariable manifestation and in these particular cases had not been severe. Nevertheless such a possibility needed to be excluded. The second problem was whether, under such circumstances, an increased intake might be necessary to achieve the greatest metabolic efficiency. Abbasy et al. (1937) had shown that in infective states there was an increased utilization of vitamin C as determined by blood levels and urinary excretion. Further support for the latter possibility was to be found in the observations that the blood pyruvic acid became elevated in association with an increase in the environmental temperature (Mills, 1943) and in thyrotoxicosis (Davis and Bauer, 1944), when a raised basal metabolic rate was probably the cause.

To investigate these possibilities it was decided to follow up infants who appeared likely to have a persistently high blood pyruvic acid, that is cases of marasmus, to give such infants a trial period on a physiological dose of thiamine and then, if the blood levels remained high, to give the vitamin parenterally. If there was still no response, the next step would be to give massive doses of thiamine either orally or parenterally.

A second type of case chosen for study as possibly having a high pyruvic acid was those infants with haemolytic anaemia. Sinclair (1939) reported that haemin destroyed thiamine. In a previous paper Allibone and Finch (1945) had found a very low urinary thiamine excretion following successive doses of the vitamin in two cases with haemolytic anaemia.

With regard to the first type of case studied, it was naturally impossible to be sure that a high initial pyruvic acid level would remain elevated long enough to enable the experiment to be concluded. In a number of cases a decrease in the blood pyruvic acid coincided with a clinical improvement which made it difficult to decide the cause of the fall. A number of cases were, however, satisfactory for the purpose required and are summarized below.

In order to obtain comparable figures, the same technique of sampling and estimation of the pyruvic acid was followed as was used in an earlier study (Allibone and Finch, 1946). The specimens of blood were collected immediately before the mid-day feed. The pyruvic acid was estimated by a modification of the Neuberg-Case method.

Case Reports

Case 1, suffering from congenital syphilis, showed the persistence in a chronic infection of a high pyruvic acid uninfluenced by thiamine either orally or parenterally.

G. E. whose birth weight was 7 lb. (3,175 g.) and who was the first-born, was admitted at the age of two months weighing 9 lb. (4,082 g.). For the past month he had been fretful, had had diarrhoea, and had been noticed to go a waxy colour from time to time. On admission he was poorly and feverish. The abdomen was slightly distended, and both spleen and liver were enlarged to a depth of three fingers' breadths below the costal margin. The haemoglobin was 5·95 g. per 100 ml., erythrocytes 2·5 millions, reticulocytes 4·7 per cent. The child was originally considered to be a case of haemolytic anaemia. His condition, however, rapidly deteriorated, the abdomen becoming more distended, tense and tender. The respirations were grunting as if he were in pain. The question of peritonitis was raised, and he was put on penicillin and given a transfusion of 225 ml. blood over a period of two days (fig. 1). Five days after admission, when the mother's blood Wassermann was reported to be positive, he was put on sulpharsphenamine and the

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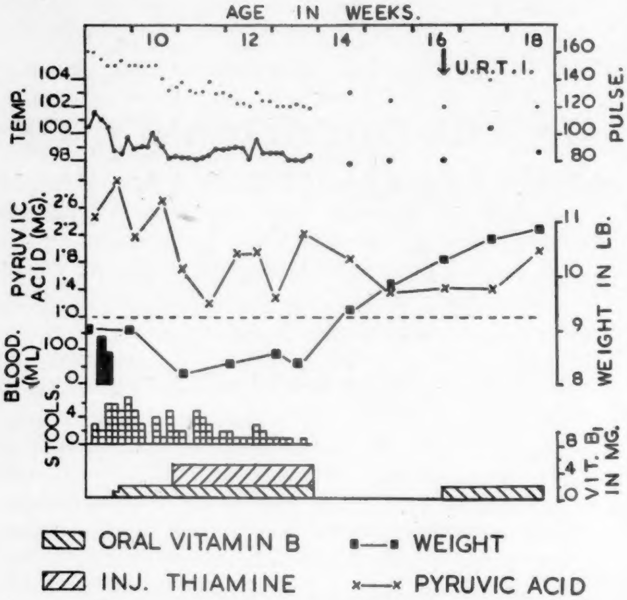

FIG. 1.—The persistence in a chronic infection of a high pyruvic acid level uninfluenced by thiamine orally or parenterally (case 1).

penicillin was increased from 48,000 units to 100,000 units intramuscularly daily. He remained poorly and febrile for twelve days. The temperature then came down but did not settle completely, nor was weight gained. The blood pyruvic acid fluctuated similarly and did not seem to be influenced by vitamin B given orally (thiamine 2 mg., riboflavin 2 mg., nicotinic acid 30 mg. in two doses daily) or intramuscularly. After discharge weight was slowly gained, but the blood pyruvic acid remained raised above 1·40 mg. per 100 ml., in association with an attack of coryza accompanied by anorexia and vomiting, culminating in otitis media.

Case 2 showed the raised blood pyruvic acid level associated with a metabolic disturbance and also the questionable effect of vitamin therapy.

B. S. was admitted at the age of three weeks with parenteral diarrhoea due to skin sepsis. The birth weight was 6½ lb. (2,950 g.). Investigations were started three weeks after admission when the baby was recovering from the diarrhoea. The weight was then 6 lb. (2,720 g.). Twenty days later the diarrhoea recommenced, the pyruvic acid level remained raised, fluctuating about 1·8 mg. per 100 ml. Weight gain ceased (fig. 2). With the cessation of the bowel disturbance there followed a more rapid increase in weight accompanied by a fall in the pyruvic acid level to 1·0 mg. At the onset of the experiment, two tablets of yeast were given three times a day which was equivalent to 1·8 mg. thiamine daily. (three tablets, weighing 1 g., contained thiamine 0·9 mg., riboflavin 0·05 mg., nicotinic acid 0·25-0·35 mg., and piridoxin 0·025-0·050 mg.). After thirteen days this was changed to thiamine intramuscularly, 70 microgrammes being given eight-hourly for a further fourteen days. As this had no effect, thiamine, 1 mg., was administered orally seven times a day after feeds. Twelve days later the thiamine was given intramuscularly, 1 mg. eight-hourly. After an interval of seven days the blood pyruvic acid now began to fall.

COMMENT. The fall in the blood pyruvic acid level was associated with an improvement in the clinical condition as shown by the decrease in the number of stools and the gain in weight. The effect of the vitamin therapy is uncertain. The cause of the relapse remained obscure. There was at no time any pyrexia nor was a parenteral cause found.

Case 3 illustrated the failure of thiamine to reduce the raised blood pyruvic acid level in a chronic infection which ended fatally.

P. M., a female infant, was admitted at the age of two months with a history of jaundice dating from the age of two weeks. The birth weight was 6 lb. (2,720 g.), the weight on admission was 8½ lb. (3,850 g.). Development was fairly good; the liver and spleen were just palpable. There was a moderate degree of jaundice, the blood bilirubin being 3·2 mg. per 100 ml. Bile pigments were present in the stools. Haemoglobin was 9·9 g. per 100 ml., red cells 3·6 millions, reticulocytes 3·6 per cent.

After the baby had been in hospital for nearly three weeks, she suddenly developed a temperature which did not settle. The Mantoux reaction was

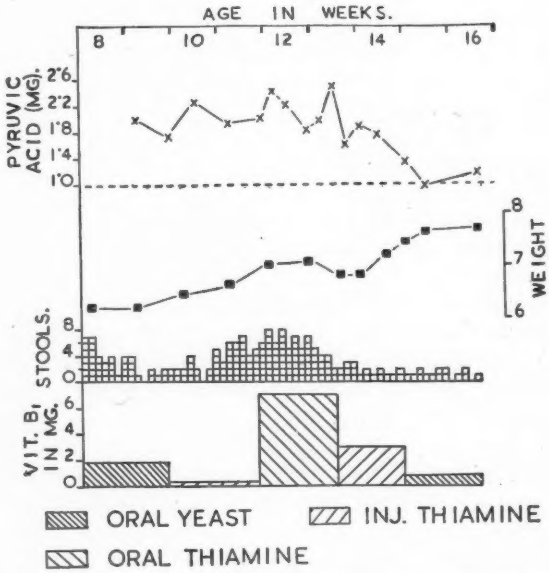

FIG. 2.—A persistent raised blood pyruvic acid associated with a metabolic disturbance. The questionable effect of vitamin therapy (case 2).

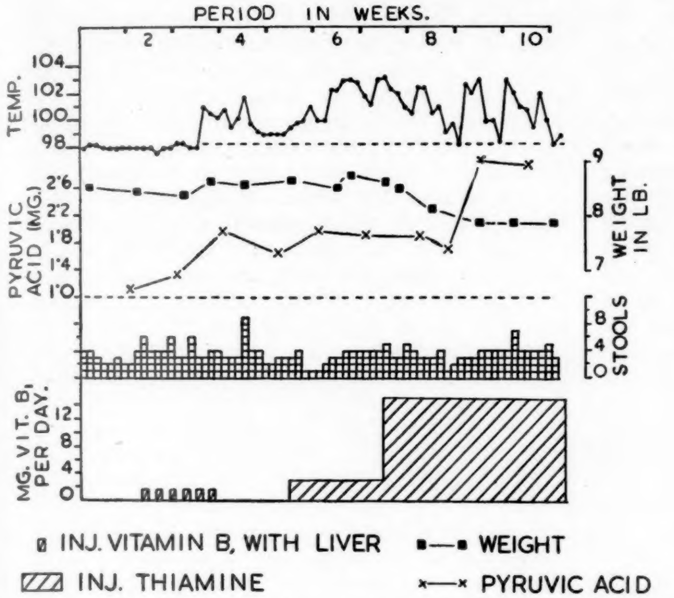

FIG. 3.—The failure of thiamine to reduce the raised blood pyruvic acid level in a chronic infection with a fatal termination (case 3).

positive and a radiograph of the chest suggested a tuberculous bronchopneumonia.

With the onset of the pyrexia the pyruvic acid level, which had been only slightly elevated, rose to nearly 2·0 mg. per 100 ml., at which level it remained in spite of parenteral injections of 1 mg. thiamine eight-hourly for fourteen days, followed by injections of 5 mg. eight-hourly for a further twenty-six days. There was a terminal rise of the blood pyruvic acid to 3·0 mg. in spite of continued high vitamin therapy (fig. 3). At autopsy the primary focus was found to be in the right lung.

COMMENT. Although the pyrexia, by elevating the metabolic rate, may have been a factor in the causation of the high blood pyruvic acid, the level had begun to rise before any fever had been recorded. The daily optimal requirements of thiamine, calculated at 0·02 mg. per lb. body weight (Knott et al., 1943), were less than 0·20 mg. If a raised metabolic rate had been an important cause, the initial parenteral dose of 3 mg. per day would have been amply adequate to restore normality. The blood pyruvic acid level remained uninfluenced not only by this dose but also by the massive amount of 15 mg. a day. The terminal rise in the level gave evidence of an impending metabolic eclipse. One must assume in this instance that either a deficiency in thiamine had little to do with the disordered carbohydrate metabolism or that the body was incapable of using the vitamin even when given in large doses.

Case 4 showed the effect on the blood pyruvic acid of an intercurrent infection and also the failure of either oral or parenteral vitamin to achieve normality in the presence of residual sepsis.

P. V. was admitted aged eight months with one week's history of cough, diarrhoea, and vomiting. She had on clinical examination an upper respiratory tract infection which was treated with penicillin, 3,000 units three-hourly for thirty days, and with succinyl sulphathiazole, 1·0 g. four-hourly for twenty-five days. Parenteral fluids were given initially. The diarrhoea settled down after ten days, but the temperature never came down to normal, the pulse averaged 130 and the respirations remained between 39 and 40 per minute. She received throughout the greater part of her stay vitamin B given orally (thiamine 2·0 mg., riboflavin 2·0 mg., nicotinic acid 30 mg. in two doses daily). This was supplemented between the eleventh and fifty-fourth day by nine yeast tablets daily, which gave an additional intake of 2·7 mg. thiamine per day (fig. 4). (Three yeast tablets, weighing 1 g., contained thiamine 0·9 mg., riboflavin 0·05 mg., nicotinic acid 0·25-0·35 mg., and piridoxin 0·025- 0·050 mg.)

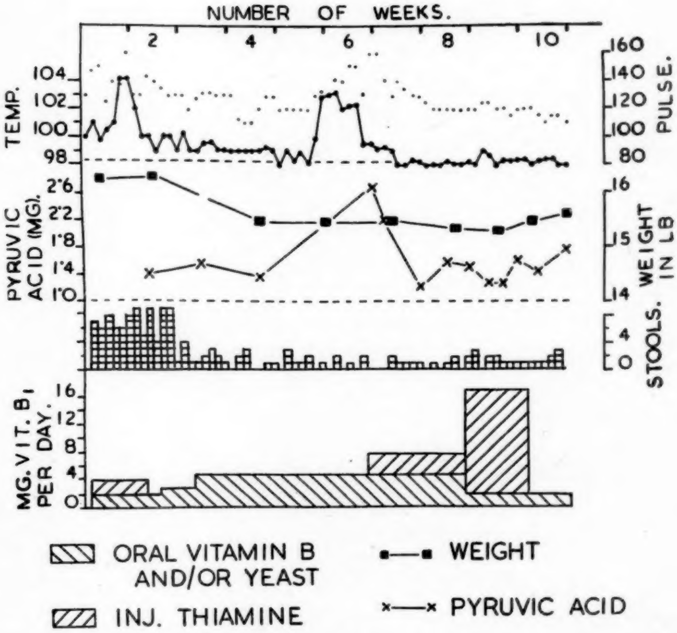

FIG. 4.—The effect on the blood pyruvic acid of an intercurrent infection. Failure of either oral or parenteral vitamin to achieve normality in the presence of residual sepsis (case 4).

On the thirty-fifth day, four days after the cessation of the penicillin treatment, acute pneumonia developed with a small empyema which was treated with another course of penicillin, 3,000 units eight-hourly for twenty-four days, and sulphadiazine, 0·5 g. six-hourly for twenty days. The blood pyruvic acid level, which had been slightly elevated before the complication, now rose to 2·60 mg. per 100 ml. of blood but came down to 1·22 mg. as the baby became afebrile. In spite of a normal temperature and normal stools, the pulse rate remained at 120, the respiration rate persisting at 60 for three weeks and still being 40 per minute on discharge. Serial radiographs of the chest demonstrated that resolution was slow; the weight remained stationary and the blood pyruvic acid showed no evidence of falling to normal figures in spite of an adequate oral intake supplemented by first a moderate parenteral dose of thiamine and finally a massive parenteral dose of 5 mg. eight-hourly.

Comment. The increased pyruvic acid after a pulmonary complication occurred in the absence of diarrhoea and in spite of a previously generous intake of the whole vitamin B complex. Parenteral thiamine had no influence on the level.

Case 5 was a further illustration of the effects of a febrile episode on the blood pyruvic acid and the questionable and certainly delayed effects of thiamine therapy.

M. C. was admitted as being allegedly of thirty-four weeks' gestation. Weight on the fourth day was 3 lb. 11 oz. (1,676 g.). He fed well from birth. Jaundice was present between the third and eighth days. The feed was diluted breast milk with added casein hydrolysate and dextrimaltose.

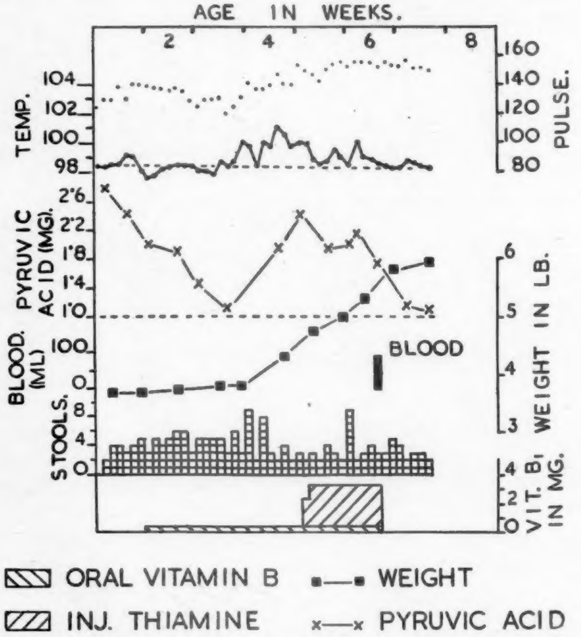

Fig. 5.—The effect of a febrile episode on the blood pyruvic acid. The questionable and certainly tardy effects of thiamine therapy (case 5).

Although there was no initial gain in weight, the temperature and pulse were satisfactory. The baby seemed well. The blood pyruvic acid level, which on the second day was 2·78 mg. per 100 ml., fell steadily until by the nineteenth day it had reached 1·12 mg. (fig. 5). Two days after this the baby became pyrexial, the pulse rate rose, and feeds were taken unwillingly. The condition was treated as one of infection, though the onset of the disturbance coincided with a heatwave which affected three other premature babies in a similar way though to a less degree. There was a concomitant rise in the blood pyruvic acid to 2·40 mg. per 100 ml. and weight began to be gained rapidly, which appeared strange until, on the thirty-fifth day, clinical oedema became obvious. The oedema persisted in varying degree and did not seem to be associated in itself with any constitutional disturbance. The baby's clinical condition now improved steadily, the oedema gradually disappeared following a blood transfusion, and the blood pyruvic acid eventually fell to normal.

Comment. The initial high blood pyruvic acid was an exaggerated example of the high levels which occur in full-term babies during the first week of life. In view of the precarious state of the premature baby's metabolic equilibrium, such high figures are no occasion for surprise.

The second fall in the blood pyruvic acid level came at the end of the febrile episode when the clinical condition improved greatly. If the thiamine injections contributed to this fall, the response was delayed. It had previously been noticed that a blood transfusion frequently lowered the level, and for that reason the vitamin therapy was stopped as soon as the transfusion had been given.

Case 6 showed the effect of the whole vitamin B complex on the blood pyruvic acid in a case of coeliac disease in an infant.

R. D. was admitted aged seven weeks with a history of diarrhoea. Birth weight was 5 lb. (2,270 g.), and weight on admission 4 lb. 6½ oz. (2,000 g.). He had always had difficulty with his feeds and there had been previous attacks of diarrhoea.

After the diarrhoea ceased and dehydration had been relieved, the weight remained stationary. The stools were eventually noticed to be large, pale, and somewhat offensive but not frequent, averaging three a day. At the age of thirteen weeks the fat content of the stools was 63 per cent. of the dried weight, the daily fat output weighing 6·0 g., which was equal to 35 per cent. of the fat content of the feed. The latter consisted of full cream lactic acid milk 14 oz. (400 ml.), water 10 oz. (140 ml.), and dextrimaltose 1 oz. (28 g.) per day. Trypsin was present in the duodenal juice.

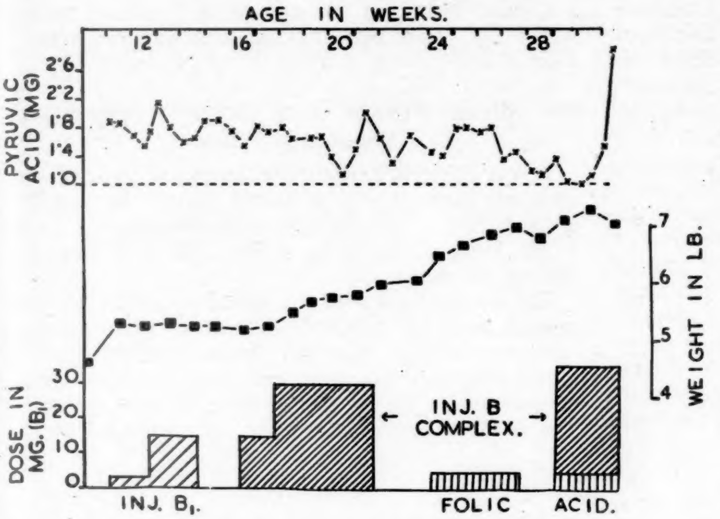

FIG. 6.—The effect of the whole vitamin B complex on the blood pyruvic acid level in a case of coeliac disease in an infant (case 6).

The general condition was reasonably good apart from marasmus and some pallor. The blood pyruvic acid remained elevated, ranging between 1·5 and 2·0 mg. per 100 ml. (fig. 6). An intramuscular injection of thiamine hydrochloride, 1 mg., was given eight-hourly for eleven days, when the dose was increased to 5 mg. eight-hourly for a further fourteen days. This was without demonstrable clinical or metabolic effect. After an interval of twelve days intramuscular injections of vitamin B complex were given (1 ml. contained 10 mg. of thiamine, 0·5 mg. riboflavin, 25 mg. niacin amide, 0·5 mg. piridoxin, 0·5 mg. calcium pantothenate). Initially 1·5 ml. was given daily for the first ten days. The dose was then doubled and continued for a further twenty-eight days. The weight now began to increase and continued to do so, though slowly. The pyruvic acid fluctuated between 1·13 and 2·0 mg. per 100 ml. of blood. When the baby was twenty weeks old the fat comprised 57 per cent. of the dried stool, the daily faecal fat excretion of 4·4 g. being 24 per cent. of the fat ingested. After a rest from therapy for sixteen days, he was given 5 mg. folic acid orally daily for twenty-five days, by the end of which period the blood pyruvic acid had gradually fallen to 1·20 mg. per 100 ml. The faecal fat comprised 42·5 per cent. of the dried stool. The daily output of 2·0 g. was equivalent to 11 per cent. of the fat intake. Following another therapeutic rest period of ten days the folic acid, orally and in the same dosage, was administered for eighteen days together with daily intramuscular injections of 3·0 ml. of the preparation of vitamin B complex previously given. Within a week the pyruvic acid, for the first time since the investigation started, fell to 1·0 mg. per 100 ml. blood. The pyruvic acid level now began to rise without any apparent reason, and within a week reached what was for this case a record height of 2·90 mg. The temperature, pulse, and respiration remained normal, though the weight fell from 7 lb. 7 oz. (3,360 g.) to 7 lb. 1 oz. (3,190 g.) within three days. The following day he was taken home at the parent's request. Twenty-four hours later he choked while being fed and died. Autopsy revealed enteritis, toxic hepatitis and chronic interstitial pneumonia. Histologically the pancreas was normal as were the other organs except those mentioned above.

COMMENT. In this infant, who was the youngest case of coeliac disease diagnosed at this hospital, the raised pyruvic acid may have been due to a deficiency of factors all of which were contained in the vitamin B complex, including the folic acid. In the presence of his terminal infection they were, however, incapable of maintaining equilibrium. Of interest is the absence of any clinical evidence that he was going downhill, apart from the loss in weight, yet the blood pyruvic acid had been rising for four days before he died.

Case 7 was a further demonstration of the effects of a complication on the intermediate metabolism of carbohydrate.

T. D. was admitted at the age of three weeks with parenteral diarrhoea due to an upper respiratory

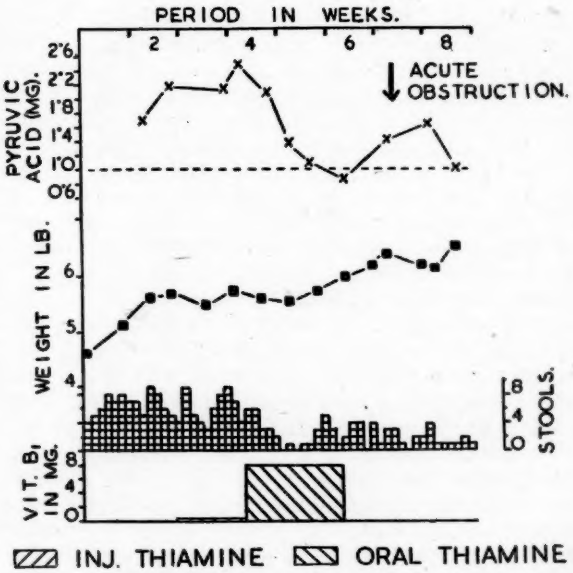

FIG. 7.—Demonstration of the effect of a surgical complication on the intermediate metabolism of carbohydrate (case 7).

tract infection. After hydration had been achieved, the weight remained stationary until the diarrhoea ceased in the fourth week, after which weight was gained. Commencing on the fourteenth day, 0·07 mg. thiamine hydrochloride was given by intramuscular injection eight-hourly for ten days without appreciable effect. The total daily requirement of thiamine was about 0·12 mg. This therapy was followed by 1 mg. thiamine orally eight times daily after feeds. It coincided with the cessation of the diarrhoea and with a fall of the pyruvic acid to a normal level of 0·87 mg. (fig. 7). When treatment was stopped the blood level rose instead of remaining down, as one would have expected in view of the improvement in the clinical condition as reflected in the cessation of diarrhoea and commencing weight gain. On the forty-fifth day after admission a large right inguinal hernia, which had been present before coming into hospital, strangulated. Though the blood pyruvic acid subsequently rose a little higher, it had fallen to a normal value of 1·0 mg. within nine days of the operation for relief of the strangulation and without the addition of extra vitamin.

TABLE 1

BLOOD PYRUVIC ACID LEVELS IN A SERIES OF NORMAL NEWBORN INFANTS DURING THE FIRST WEEK OF LIFE

Name	Age in days		
	1	4-5	7-8
Th.	2·75	1·25	1·44
Te.	2·27	1·37	0·93
Cu.	2·26	1·75	1·25
Li.	1·85	1·28	1·18
We.	1·66	1·30	1·07
Da.	1·46	1·28	1·38
Cn.	1·26	1·72	0·92

Pyruvic acid given in mg. per 100 ml. blood.

Comment. One might assume that the rise in pyruvic acid before the strangulation was due to the cessation of oral therapy. It must, however, be remembered that cows' milk, even after allowing for loss in pasteurization, still contains approximately twice the quantity of thiamine in human milk (Lawrence et al., 1945). At this phase the diarrhoea had settled and weight was being gained. There was no deficiency of thiamine in the diet and no apparent call for extra vitamin. That the dietary intake was adequate under normal circumstances was seen by the return to normal values once recovery from the effects of the obstruction had occurred. Although the idea may at first appear improbable, it seems as if the rise in the blood pyruvic acid at this time was associated with a metabolic disturbance which found its clinical culmination in acute intestinal obstruction. This elevation of the pyruvic acid level occurring before a clinical event, in the nature of 'writing on the wall,' was also seen in the ante-mortem rise in cases 3 and 6.

The Blood Pyruvic Acid Level in Haemolytic Anaemia in Infancy

It was possible to estimate the blood pyruvic acid in seven cases of icterus gravis during the first five days of life. The figures were respectively 1·16, 1·92, 1·86, 3·26, 1·93, 1·50, and 2·06 mg. per 100 ml. of blood.

The interpretation of the raised pyruvic acid level in such cases was rendered difficult by the numerous factors involved. Normal newborn infants have a raised blood pyruvic acid which usually approaches normal values by the end of the first week (table 1). The toxic action on the liver, as evidenced by the deep jaundice, in icterus gravis may affect pyruvate metabolism as the liver and kidney convert thiamine into its active form, cocarboxylase. Liver damage has been shown to interfere with thiamine metabolism (Allibone and Finch, 1945). Davis and Bauer (1944) found raised blood pyruvic acid levels in hepatic disease.

TABLE 2

BLOOD PYRUVIC ACID LEVELS IN CASES WITH HAEMOLYTIC ANAEMIA WITHOUT JAUNDICE

Name	Cause of anaemia	Age in days	Hb. on admission	Reticulocytes (%)	Pyruvic acid mg. %
J.W.	H.D.N.B.	57	52	9·0	2·50
S.B.	„	27	47	34·8	3·50
R.M.	„	73	64		3·10
B.B.	„	45	65		1·85
D.E.	?	56	42	13·2	2·35
M.K.	Nephritis	92	42	14·6	1·88

H.D.N.B. = Haemolytic disease of the newborn.

In view of the difficulty of assessing the significance of the raised blood pyruvic acid in icterus gravis during the first week of life, six older infants were collected who had a haemolytic anaemia, but no jaundice. Three cases had had icterus gravis and were admitted with an exacerbation of the haemolytic process; in one case there was an acute haemorrhagic nephritis thought to be a sequel to a streptococcal tonsillitis. In two the cause was unknown. All infants in this group had a raised blood pyruvic acid, the average figure being 2·53 mg. per 100 ml. of blood (table 2).

After a blood transfusion the blood pyruvic acid fell in every case except one. The level, however, rose immediately in those cases where the haemolytic process persisted, necessitating further transfusion, or where a toxic or infective state complicated the picture. The results of blood transfusion on the pyruvic acid level in cases of haemolytic anaemia

TABLE 3

EFFECT OF BLOOD TRANSFUSION ON THE BLOOD PYRUVIC ACID LEVEL IN CASES OF HAEMOLYTIC ANAEMIA

Disease	Name	Pyruvic acid before transfusion		Blood given		Pyruvic acid after transfusion	
		Level in mg.	Days	Amount in ml.	% of blood vol.	Days	Level in mg.
Nephritis	M.K.	1·88	3	340	66	3	1·57
Ict. Grav.	L.B.	1·47	1	120	45	4	1·17
		1·17	1	96	34	3	1·33
,, ,,	R.M.	1·82	0	72	33	2	1·58
		1·58	2	80	35	2	1·07
		1·24	1	64	25	2	0·67
		3·10	0	80	20	4	1·63
,, ,,	B.B.	1·78	0	120	48	3	1·20
		1·25	2	112	43	2	0·93
		1·85	0	96	30	2	1·53
		2·03	1	80	22	3	1·38
,, ,,	J.C.	1·93	1	112	35	2	1·28
		3·30	0	96	30	4	1·80
,, ,,	A.T.	1·18	3	176	63	0	1·18
,, ,,	R.G.	2·06	0	128	49	3	1·07
H.D.N.B.	S.B.	3·50	1	72	30	1	2·50
?	D.E.	2·35	3	80	44	4	1·07
Average figures		1·97					1·35

are given in table 3. The action of persistent haemolysis in a particular infant are well illustrated in the following case.

Case 8, with icterus gravis, demonstrated the effect on the blood pyruvic acid of repeated blood transfusion.

B. B. was admitted when one day old, jaundice being noticed immediately after birth. She was the second child, the first being normal. The blood group was O Rh positive. The reactions with strong anti Rh sera were very weak, the erythrocytes being blocked by incomplete antibodies. The conglutinin test with the baby's serum was positive, as were the sensitization tests with antihuman globulin serum and with concentrated AB serum. Initially there was a rapid haemolysis, the haemoglobin falling from 104 per cent. to 50 per cent. in five days. Although the jaundice had disappeared by the fourth week and the baby was well enough to be allowed home, the haemolytic process persisted to a less degree, readmission being necessary in the seventh week and four transfusions being given in all before a stable blood picture was achieved (fig. 8). After each transfusion there was a fall in the blood pyruvic acid, this being only temporary in the case of the first three transfusions.

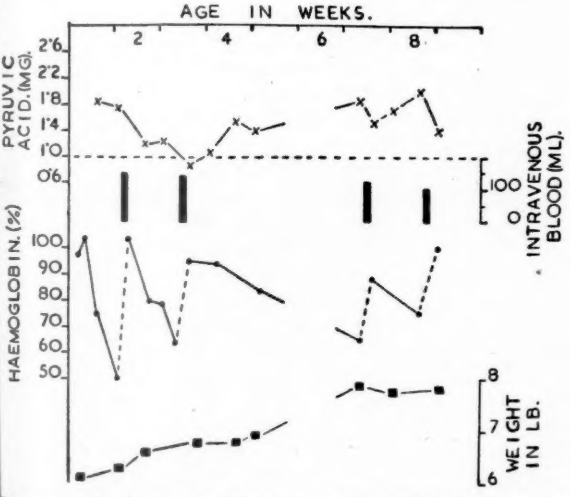

FIG. 8.—The lowering of the blood pyruvic acid by blood transfusion (case 8).

Discussion

Glucose, when completely metabolized to carbon dioxide and water, goes through a sequence of stages which have been identified as far as pyruvic acid. For the further breakdown there are several possible ways, dismutation to lactic and acetic acids, decarboxylation to acetaldehyde, oxidation to acetic acid or oxidation of pyruvic acid phosphate to acetyl phosphate and also conversion to oxaloacetic acid by carbon dioxide fixation. Although all these reactions occur in either lower animals or in bacteria, the method in man is as yet unknown (Stotz, 1945), but it is thought that pyruvic acid is carboxylated to oxaloacetic acid, which is then utilized in two cycles, the citric acid or the succinic acid (Bicknell and Prescott, 1946). The enzyme system catalyzing these reactions comprises a number of components which include inorganic phosphate, metallic ions, manganese, magnesium, or cobalt, protein, and one or more factors of the vitamin B complex. A number of interrelationships have been shown to exist between thiamine and the other vitamins. In chronic thiamine deficiency there is a lowered retention of riboflavin with increased loss in the urine (Sure, 1944). In rats depletion of thiamine is associated with an increased concentration of riboflavin in the liver (Singher et al., 1944). The association of biotin and pantothenic acid with pyruvic acid metabolism was shown by a decreased oxygen consumption in the presence of pyruvate by homogenates of liver from pantothenic and biotin deficient rats (Pilgrim et al., 1942). The addition of small amounts of biotin under such circumstances accelerated the removal of the substrate (Summerson et al., 1944).

An accumulation of pyruvic acid in the blood may be caused either by retardation in its breakdown to carbon dioxide and water or by failure of resynthesis to glucose. Whatever the process, the number of factors participating in these reactions are sufficiently numerous to indicate that a raised blood pyruvic acid cannot be considered synonymous with thiamine deficiency. Williams et al. (1943) considered that a high blood pyruvic acid after the ingestion of glucose signified a vitamin deficiency, provided insulin hypoglycaemia, hyperthyroidism, mild diabetes, and other factors related to carbohydrate metabolism could be excluded. On the grounds given in the previous paragraph, this manoeuvre does not render the test more specific although it may become more delicate. Lu and Platt (1939) achieved a similar effect by estimating the blood pyruvic acid after exercise.

In none of the infants in this series of cases was there reason to suspect beriberi nor could either clinical or metabolic improvement be definitely attributed to the vitamin therapy. On the other hand cases of beriberi respond dramatically to thiamine. Platt and Lu (1939) found that the removal of pyruvic acid from the blood on giving thiamine was initiated after a lag of about four hours, the time interval being due to the conversion of thiamine into its active form cocarboxylase. In adults with acute beriberi a single dose of from 5 to 10 mg. of thiamine reduced blood pyruvate levels of 3·0 to 5·0 mg. to normal in about ten hours. In a fatal case of a boy with congestive heart failure due to beriberi, with cirrhosis of the liver and terminal pericarditis, previously reported by Allibone and Baar (1946), 12·5 mg. thiamine was given by intramuscular injection in divided doses daily. The blood pyruvic acid fell from 1·97 to 1·13 mg. per 100 ml. in twenty-four hours. Three days later, on the day before death, it was 0·70 mg. (fig. 9). In view of the imminence of his decease it is remarkable that the blood pyruvic acid level was affected at all. This result contrasted with the effect of intramuscular injections of thiamine given in cases 1, 2, 3, and 5, where no fall in the blood pyruvic acid occurred. In case 4 the level began to fall after a lag of seven days following the administration of intramuscular thiamine equivalent to 500 microgrammes per lb. body weight. Yeast, the calculated daily optimum dose of thiamine given intramuscularly, and massive oral thiamine therapy all failed to influence the pyruvic acid level in case 2. During the administration of thiamine intramuscularly in larger doses equivalent to 500 microgrammes per lb. body weight, the level began to fall after an interval of seven days.

The difference in the response of the blood pyruvic acid to the administration of thiamine, between these cases of marasmus and chronic infection in infancy on the one hand and those cases of beriberi on the other, left no doubt that thiamine deficiency played little part in the etiology of the raised level in the former. Owing to the relationship between thiamine and the other components of the vitamin B complex, the possibility existed that a lack of part of the remaining or thermostable fraction might be responsible for the abnormality in carbohydrate metabolism in these cases. That this might be so was suggested from the course of R. D. (case 6), the infant with coeliac disease, whose blood pyruvic acid seemed to be settling to normal when he was given vitamin B complex plus folic acid. The fall was, however, in no way dramatic, and the rapid antemortem rise while the child was still receiving treatment showed his metabolic instability. Further, the treatment of sixteen cases of coeliac disease with high doses of vitamin B complex, 4 ml. intramuscularly every other day for three and in some cases six weeks, produced no change in the blood pyruvic acid (Allibone, 1946). (1 ml. contained 10 mg. thiamine, 0·5 mg. riboflavin, 25 mg. niacin amide, 0·5 mg. piridoxin, 0·5 mg. calcium pantothenate.) It cannot, therefore, be maintained that the breakdown in carbohydrate metabolism in the infants under

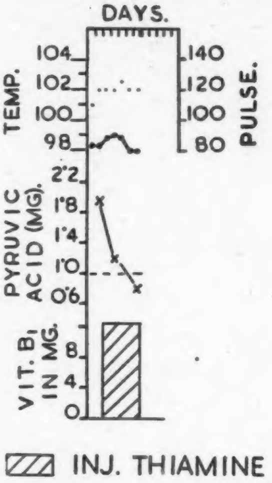

FIG. 9.—The rapid fall in the blood pyruvic acid in a case of beriberi following treatment with Vitamin B_1.

discussion could be attributed to a deficiency of any of the known components of the vitamin B complex. Whatever may be the cause, its elucidation will contribute materially to the understanding of the mechanism of the intermediate metabolism of glucose.

The raised blood pyruvic acid in the newborn was not thoroughly investigated. Although the probable cause was a temporary disorganization of metabolism following birth, other possibilities have to be considered. In rabbits (Lu, 1939) and in man (Johnson and Edwards, 1937) the blood pyruvic acid is raised after exercise. It is likely that during labour the blood pyruvic acid in the mother will be raised, and that this increase would be shown in the blood of the newborn. As normal values are reached again within an hour after exercise, this factor should not operate after the first day.

The presence of ketosis will give high values. The colorimetric method used for the determination of pyruvic acid was based on the isolation of sodium pyruvate 2,4-dinitrophenylhydrazone and the reaction of the latter with strong alkali to form a red derivative. The corresponding hydrazones of acetone and acetoacetic acid give a similar red colour with alkali. As a result a ketosis gave erroneously high values for pyruvic acid. It was, therefore, our practice to abandon the estimation in the presence of ketonuria. Sometimes, however, it was impossible to obtain a specimen of urine in a newborn infant, particularly in a female. Bueding et al. (1941) suggested that allowing the ethyl acetate extract to stand overnight in the refrigerator would allow the hydrazones of acetoacetic acid and acetone to be destroyed. The writer's experience with this modification of the method was not successful. In cases with ketonuria, after a duplicate had stood overnight, the result next day was on several occasions even higher than the sample estimated the day before. Klein (1941) substituted tungstic acid for trichloracetic acid as the protein precipitant and allowed the ethyl acetate extract to stand for eighteen to twenty-four hours in the refrigerator. In this way the acetoacetate hydrazone decomposed, leaving the pyruvate hydrazone intact. This modification is indicated whenever there is a likelihood of ketosis being present.

The causation of the high pyruvic acid level in haemolytic states may be due to several factors not previously discussed. Evidence for the destructive action by a haemolytic process on thiamine in the blood has been given. Where the haemoglobin has fallen considerably, the anoxaemia may interfere with the oxidation of pyruvic acid. The toxaemia associated with the haemolysis may depress not only those enzymes concerned with the disintegration of pyruvic acid but also those which may help to resynthetize the acid to glucose. This concept was supported by the lack of response of the blood pyruvic acid to blood transfusion in those cases with a severe constitutional disturbance, as was seen in G. E. (case 1). The possibility that the fall might be a dilution phenomenon, due to a low pyruvic acid in the donor's blood, had to be considered. The occasional high blood pyruvic acid following transfusion was against such an explanation. The pyruvic acid level in stored blood from a healthy donor depended on the time it had been kept in the refrigerator. It appeared that the catabolism of glucose continued as far as the pyruvic acid stage rather faster than beyond it. The pyruvic acid, in consequence, rose for about a week and then, all sources of pyruvic acid having been exhausted, the level began to fall (table 4). Blood from a healthy donor, therefore, contains potentially the same amount of pyruvic acid during the first week of storage. As the pyruvic acid estimation following transfusion was usually performed after an interval of two to three days, adequate time was allowed for stabilization to take place. In normal animals an excess of pyruvate can be removed from the blood in half an hour (Lu, 1939). It seems, therefore, probable that the transfused blood, by removing or mitigating one or more of the causes contributing to the raised level in the patient's blood, was able to produce a temporary fall in the patient's blood level in the not too severe cases (B. B., case 8) and even initiate or potentiate a permanent reduction in those cases which had entered into the stage of convalescence, as with M. C., case 5.

TABLE 4

THE EFFECT OF STORAGE IN A REFRIGERATOR ON THE PYRUVIC ACID LEVEL IN BLOOD TAKEN FROM A HEALTHY DONOR

Name	Duration of storage in days			
	0	3	6	10
Gl	0·93	2·27	2·63	1·63
Ha	1·13	2·34	2·69	1·72

Pyruvic acid in mg. per 100 ml.

There seems little doubt that the disordered intermediate carbohydrate metabolism, as evidenced by an elevation of the blood pyruvic acid, which is seen in toxaemic and haemolytic states in infancy, is not due to deficiency of vitamin B. On the other hand the raised blood pyruvic acid level in beriberi falls quickly when thiamine is given. It is suggested that, where in any case the resting blood pyruvic acid is raised, the response of the level to the administration of vitamin B would constitute a therapeutic test for the presence or otherwise of a deficiency of the vitamin.

Lu (1939) found no abnormality of the resting blood pyruvic acid in cases of the 'atrophic type' of beriberi, which presented only nervous manifestations, although after exercise the raised level returned to normal more slowly than in healthy individuals (Lu and Platt, 1939). Bueding et al. (1941) reported that when glucose was given to thiamine-deficient subjects, the blood pyruvic acid rose to a higher level and remained elevated for a longer period than was the case with controls. If this test were to be performed before and after saturating the body with vitamin B, it should distinguish subclinical states of true vitamin deficiency from other conditions causing dysfunction of intermediate carbohydrate metabolism.

Summary

The raised blood pyruvic acid level encountered during infancy in toxaemia and haemolytic states is not associated with a deficiency of thiamine and is probably unrelated to any of the known factors in the vitamin B complex.

The implication of the above findings in relation to the intermediate metabolism of carbohydrate is discussed.

A test for the diagnosis of subclinical states of thiamine deficiency is suggested.

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PUBERTY GROWTH OF BOYS

BY

RICHARD W. B. ELLIS, M.D., F.R.C.P.

(From the Department of Child Life and Health, University of Edinburgh)

In a previous communication (Ellis, 1946), a comparison was made between the mean heights and weights of groups of boys of the same year of age but of different stages of maturity. The comparisons were limited to boys resident in the same school where dietetic and environmental conditions were standardized. It was shown that, between the ages of 11 and 16, the mean heights and weights of boys given a higher maturity-grading were significantly greater than those of less mature groups of the same age. In addition, it was found that when the mean heights and weights of the groups compared were plotted retrospectively, the earlier-maturing boys were on the average taller and heavier in each year for which records were available, that is, for several years before manifestations of pubescence appeared.

The present study represents a follow-up of 154 of the 208 boys originally graded, with particular reference to height and weight increments over a twelve-month period related to the various stages of maturity recognized. Since the purpose of the study was essentially to see whether different rates of growth could be demonstrated for different stages of maturity, little emphasis has been placed on chronological age. The present groups compared are therefore not identical with those compared in the previous study; within the age-ranges studied, it has not been considered necessary to subdivide the physiological (developmental) age-groups into year-age-groups, except in one instance (School A) where this was done as a double check on the general findings.

Clinical material. This comprised 154 boys from two residential schools, 101 from School A (aged 12 to 15½ in March, 1946), and 53 from School B (aged 14 to 16½ in July, 1947). None of those included had suffered from recent or prolonged illness likely to have affected growth. Comparisons were again only made between boys resident in the same school, in order to avoid as far as possible differences attributable to diet and environment.

Experimental period. In the case of School A, this ran from March 24, 1946, to March 24, 1947; in the case of School B, from July 16, 1946, to July 16, 1947. The boys in School A were weighed, measured, and graded in March, 1946, and again one hundred days later; they were finally reweighed, remeasured, and regraded in March, 1947. The boys from School B were weighed, measured, and graded in July, 1946, and again in March, 1947. They were reweighed and remeasured in July, 1947. The previous heights and weights of the fifty-three boys in School B were available for July, 1944, and July, 1945, and from these the annual growth increments for the two years preceding the original grading have been calculated.

Maturity-grading. The criteria employed for maturity-grading have already been described (Ellis, 1946), and their validity discussed. Three maturity grades were recognized, viz. (1) ' pre-pubescent ' or ' non-pubescent ' (the latter term being preferred here to avoid confusion with the nomenclature of other authors, which unfortunately is not uniform); (2) ' pubescent '; and (3) ' adolescent.' The transition from pubescence to adolescence is assumed to correspond approximately with onset of spermatogenesis, though this is not essential to the main purpose, which is to recognize clinically and compare three grades of increasing maturity. In the earlier studies of maturity related to growth, intellectual achievement, and physical performance carried out during the present century, various clinical criteria for maturity-grading of children were used (Crampton, 1908; Baldwin, 1921; Davenport, 1926). In the case of boys, particular attention has usually been paid to the appearance of pubic and axillary hair respectively as indicating successive degrees of maturity. Thus Richey (1937) took the appearance of axillary hair as indicative that boys had attained puberty, and classified subjects on this basis. Subsequently Greulich et al. (1942) considered all the clinical manifestations of puberty in considerably more detail, and systematized the classification of boys into five maturity grades. The present study served to illustrate the unreliability of appearance of pubic and axillary hair as sole criteria in grading, and most of the other manifestations described by Greulich were used in establishing the three grades here employed. It was realized that if the standards were to be applicable to routine school medical examinations they must be kept relatively simple, whilst at the same time making it possible to classify the cases in which the appearance of body-hair bore an atypical relationship to genital development, for example the appearance of axillary before pubic hair or testicular enlargement.

Although it became clear that it would usually be possible to distinguish on clinical grounds between early and late adolescence, it was considered inadvisable to make this sub-division after the original grading had been carried out.

Measurements. Particulars of measurement of height and weight have already been given (Ellis, 1946). As far as possible, these were carried out at approximately the same time of day, and though it is recognized that the same individual may show variations in both height and weight within twenty-four hours, it is considered that such variations are negligible when increments are considered over a twelve-month period. In the case of School A, measurements were also made of leg-length (anterior superior iliac spine to tip of internal malleolus, with patient standing barefoot), using a flexible steel tape. During the latter part of the investigation, measurements of hip circumference at the level of the great trochanter were made. When the mean values for hip circumference in the different maturity and age groups were compared, it was clear that this arbitrary measurement (involving as it does bone, muscle, and subcutaneous tissue) showed a very much closer correlation with maturity than with age; and it is suggested that in future developmental studies it might usefully be employed (Ellis, 1947b).

Results

The findings in the case of School A and School B will be presented separately, and an attempt then made to draw general conclusions from the two sets of figures.

School A. There were available for re-examination in March, 1947, twenty-four boys aged 12 to 13 years, seventy-two boys aged 13 to 15 years, and five boys over 15. It was decided to group the boys within the first two age-ranges into (1) those graded as non-pubescent on first and final examination, (2) those non-pubescent on first and pubescent on final examination, (3) those pubescent on first and final examination, (4) those pubescent on first and adolescent on final examination, and (5) those adolescent on first and final examination. The five boys over 15 are considered individually (fig. 2).

Table 1 shows the increase in height, weight, and leg-length of the respective groups over the twelve-month period, and in table 2 is shown the significance of the differences in height and weight increments observed between different maturity-groups within the same age-range.

The usual level of significance, $P = 0 \cdot 05$, has been adopted. The two groups of 13 to 15 year-old boys, who were either non-pubescent becoming pubescent, or pubescent throughout the year period, have not been compared, as there is clearly no significant difference between their rates of growth. With the single exception of the two most mature groups (pubescent-adolescent and adolescent-adolescent), who show no significant difference in height increment, it will be seen that in each comparison the increase in both height and weight is significantly greater in the more mature group than in the less mature group in the same age-range.

The mean height and weight gain of the two groups of boys who remained non-pubescent throughout the year are closely similar, viz. 4·8 and 4·3 cm. and 2·67 and 2·80 kg. respectively.

The three groups who were pubescent on the final examination, and who had either passed from non-pubescence to pubescence, or remained pubescent, throughout the twelve months, again show closely similar increases in height, viz. 6·2, 6·1, and 6·0 cm. and comparable increases in weight, viz. 3·76, 4·75, and 4·65 kg. respectively. In all cases, these increases are significantly greater than those shown by the boys who remained non-pubescent.

The boys who passed from pubescence to adolescence, and those who were adolescent on both examinations, show an increase in height which is nearly double and an increase in weight which is more than double that of the boys who remained

TABLE 1

MEAN INCREMENTS OF HEIGHT, WEIGHT, AND LEG-LENGTH OF MATURITY-GROUPS (SCHOOL A) FROM MARCH, 1946, TO MARCH, 1947

Group No.	No. of Boys	Maturity-grading		Mean Age (March, 1947)		Increase height (cm.)			Increase weight (kg.)			Increase leg-length (cm.)		
		March, 1946	March, 1947	Yrs.	Mos.	Mean	Standard deviation	Standard error	Mean	Standard deviation	Standard error	Mean	Standard deviation	Standard error
1	18	Non-pubescent	Non-pubescent	12	5	4·8	0·67	0·16	2·67	0·83	0·20	2·7	1·36	0·32
2	6	Non-pubescent	Pubescent	12	10	6·2	0·86	0·35	3·76	0·74	0·34	3·2	1·36	0·21
3	25	Non-pubescent	Non-pubescent	13	8	4·3	0·90	0·18	2·80	0·87	0·17	1·9	1·07	0·56
4	14	Non-pubescent	Pubescent	14	4	6·1	1·49	0·40	4·75	1·31	0·35	2·9	1·12	0·30
5	16	Pubescent	Pubescent	13	10	6·0	1·65	0·41	4·65	2·00	0·50	2·9	1·86	0·46
6	9	Pubescent	Adolescent	14	5	8·9	1·11	0·37	7·12	1·40	0·47	3·5	1·80	0·60
7	8	Adolescent	Adolescent	14	10	8·3	0·84	0·30	9·19	1·13	0·46	4·5	1·52	0·54

TABLE 2

SIGNIFICANCE OF DIFFERENCES IN HEIGHT AND WEIGHT INCREMENTS BETWEEN MATURITY GROUPS (SCHOOL A)

Maturity-grading.		Age-range (years)	P significance	
March, 1946	March, 1947		Height	Weight
Non-pubescent	Non-pubescent	12–13	<0·01 significant	<0·01 significant
Non-pubescent	Pubescent	12–13		
Non-pubescent	Non-pubescent	13–15	<0·001 significant	<0·001 significant
Pubescent	Pubescent	13–15		
Pubescent	Pubescent	13–15	<0·001 significant	<0·01 significant
Pubescent	Adolescent	13–15		
Pubescent	Adolescent	13–15	>0·2 not significant	<0·01 significant
Adolescent	Adolescent	13–15		

TABLE 3

MEAN ANNUAL INCREMENTS OF HEIGHT AND WEIGHTS OF MATURITY-GROUPS (SCHOOL B) FROM JULY, 1944, TO JULY, 1947

		Maturity-grading			Height increment (cm.)								
					July, 1944-July, 1945			July, 1945-July, 1946			July, 1946-July, 1947		
Group	No. of Boys	July, 1946	March, 1947	Mean Age (years) July, 1947	Mean	Standard deviation	Standard error	Mean	Standard deviation	Standard error	Mean	Standard deviation	Standard error
I ..	7	Non-pubescent	Pubescent	14·8	4·51	0·86	0·41	3·81	1·40	0·53	6·35	0·82	0·31
II ..	7	Pubescent	Pubescent	14·9	4·90	2·00	0·76	4·72	1·40	0·53	7·44	1·54	0·58
I and II	14	Pubescent or Non-pubescent	Pubescent	14·8	4·74	1·67	0·48	4·27	1·47	0·40	6·88	1·31	0·35
III ..	19	Pubescent	Adolescent	15·3	5·61	1·86	0·43	7·22	1·87	0·43	10·29	0·86	0·20
IV ..	20	Adolescent	Adolescent	15·6	7·47	1·95	0·46	9·46	2·74	0·62	7·14	2·32	0·52
					Weight increment (kg.)								
I ..	7	Non-pubescent	Pubescent	14·8	1·81	0·61	0·27	2·17	1·43	0·54	5·77	1·38	0·52
II ..	7	Pubescent	Pubescent	14·9	2·04	1·23	0·47	2·98	1·21	0·46	6·94	1·19	0·45
I and II	14	Pubescent or Non-pubescent	Pubescent	14·8	1·95	1·03	0·30	2·58	1·39	0·37	6·35	1·38	0·37
III ..	19	Pubescent	Adolescent	15·3	2·72	1·68	0·40	5·66	2·05	0·47	10·32	2·05	0·47
IV ..	20	Adolescent	Adolescent	15·6	4·82	3·02	0·71	7·54	1·47	0·33	8·51	2·49	0·56

non-pubescent throughout. These two adolescent groups are too small, and the standard deviations too great, to show any significant difference between their respective height increments: it is, however, possible to say that the increase in height and weight in both instances is significantly greater than that, of any of the less mature groups.

Leg-length. Although the 12- to 13-year-old boys show greater increments than the 13- to 15-year-old boys of corresponding maturity, the increases in leg-length follow the same pattern as the increments in height. The groups reaching pubescence, or remaining pubescent, during the experimental period show a greater increase than the non-pubescent in the same age-range, whilst those reaching adolescence, or remaining adolescent, are greater than either of the less mature groups. The standard deviations, however, in these measurements are so great that the differences cannot be taken as absolutely significant. This is undoubtedly related to the greater difficulty in accurate measurement of such relatively small increases in length.

Simmons (1944) found in boys a greater growth rate of leg-length as compared with trunk-length from three months to fourteen years, and a measurable acceleration of trunk-length, and the absence of such an acceleration of leg-length during the pre-adolescent period. She also found that trunk growth continued after the cessation of leg growth. The present findings do not appear to confirm those of Simmons with regard to absence of acceleration of leg-length in pre-adolescence. Thus table 1 shows an acceleration of leg growth in the two most mature groups (nos. 6 and 7) as compared with leg growth in the two non-pubescent groups (nos. 1 and 3).

School B. There were fifty-six boys whose records were complete for the experimental period (July,

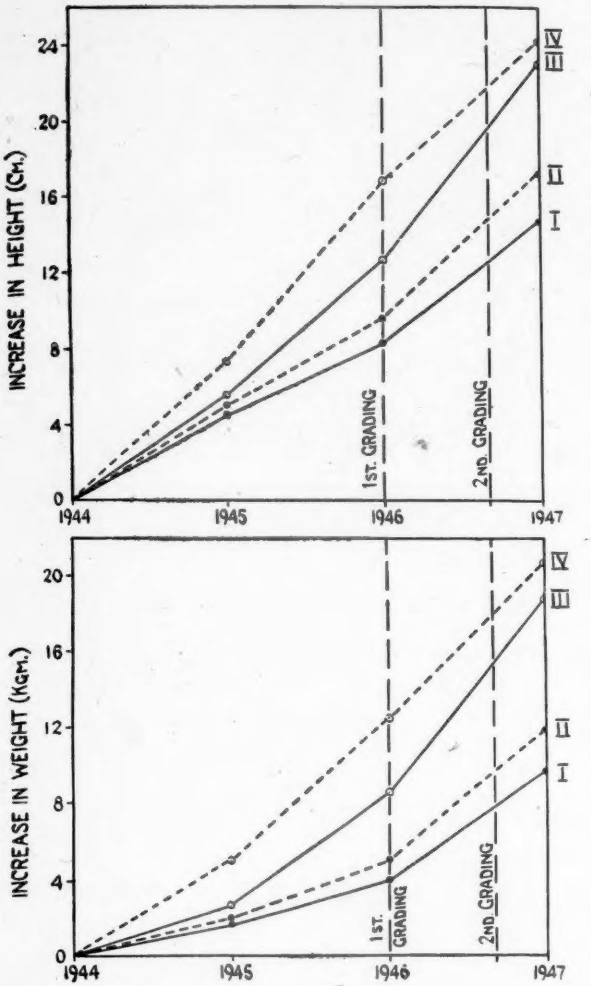


FIG. 1.—Mean annual increments of height and weight of maturity-groups (school B) from July, 1944, to July, 1947. I.—Non-pubescent on first and pubescent on second grading. II.—Pubescent on first and second grading. III.—Pubescent on first and adolescent on second grading. IV.—Adolescent on first and second grading.

1946, to July, 1947) and for the preceding two years, but as only three had remained non-pubescent throughout, they were excluded as forming a group too small for analysis.

Here the boys were aged 14 to 16½ years at the end of the experimental period, and were classified into the maturity-groups described above (p. 17) without reference to age. The mean increments in height and weight were estimated for each group for the periods July, 1944, to July, 1945; July, 1945, to July, 1946; July, 1946, to July, 1947. Although no figures can be given for boys remaining non-pubescent during the experimental period, the boys graded as non-pubescent on first examination will of course have been non-pubescent during the preceding two years, and their annual height and weight increments during these two years serve as an index of non-pubescent growth. To use growth figures obtained in 1944-46 for comparison with those of 1946-47 is open to the objection that diet may not have been the same in the three years, and the figures are used with this reservation.

TABLE 4

SIGNIFICANCE OF DIFFERENCES BETWEEN MATURITY GROUPS (SCHOOL B), JULY, 1946, TO JULY, 1947

Groups compared	P (significance)			
	Height		Weight	
I and II	$>0\cdot1$	not significant	$>0\cdot1$	not significant
II and III	$<0\cdot001$	significant	$<0\cdot001$	significant
III and IV	$<0\cdot001$	significant	$<0\cdot02$	significant

The results of this analysis are given in table 3 and fig. 1.

Table 3 and fig. 1 illustrate the following points:

1. During the experimental period (July, 1946, to July, 1947), the greatest increase in both height and weight occurs in the boys passing from pubescence to adolescence, whilst during the preceding year (July, 1945, to July, 1946) the maximum gain in height and weight occurs in the boys who were graded as adolescent in July, 1946.

2. The least mature boys (Group I) show an acceleration of increase in height and weight during the passage from non-pubescence to pubescence. This is less than the increase of the more mature groups during the same year, but is striking when compared with their own non-pubescent rate of growth in 1944-5 and 1945-6, viz. 6·35 cm. compared with 4·51 and 3·81 cm., and 5·77 kg. compared with 1·81 and 2·17 kg.

3. The growth-increments for Groups I and II combined during 1946-7 can be compared with those of Group III during 1945-6, since in each instance one is dealing with a group of boys known to be pubescent at the end of the twelve-month period (table 5).

Although too much emphasis cannot be placed on comparisons of height and weight increments of different groups in different years, the several curves do appear to establish a general pattern which is recognizable in each group. This may be described as an acceleration in increase in height and weight which is associated with (and probably precedes) the clinical manifestations of pubescence: continues throughout pubescence: and is followed by a still greater acceleration in height and weight gain with the onset of adolescence. This again continues into early adolescence, whilst the curve of Group IV during the experimental period suggests that there is a deceleration of increase in height

TABLE 5

GROWTH INCREMENTS OF GROUP I AND II COMPARED WITH THOSE OF GROUP III

	Height increment (cm.)			Weight increment (kg.)		
	Mean	Standard deviation	Standard error	Mean	Standard deviation	Standard error
Groups I and II (combined) 1946-47 ..	6·88	1·31	0·35	6·35	1·38	0·37
Group III, 1945-46	7·22	1·87	0·43	5·66	2·05	0·47

manifest in those boys who were already adolescent at the beginning of the experimental period. Rapid deceleration of increase in height normally precedes the final fusion of epiphyses which is associated with cessation of growth and attainment of full maturity. Owing to the age-range studied, the oldest boys being only 16½ years at the end of the experimental period, this deceleration would only be expected to appear in the most mature group.

Throughout the three-year period, the gain in height and weight was greater in the more mature as compared with the less mature groups. Although for purposes of comparison of the growth-increments during the three-year period, the curves have all been started from zero in fig. 1, it should be borne in mind that it had already been established (Ellis, 1946) that the mean total height and weight of more mature groups was also significantly greater than that of the less mature groups of the same age. The age-range studied was not sufficiently extensive to give any information as to whether the boys who matured late would ultimately catch up with or pass the earlier-maturing boys in height; there is considerable difference of opinion expressed by different authors on the effect of early or late maturity on adult height (Van Dyke, 1930), and there is evidently field for further study of this point, particularly in the case of boys.

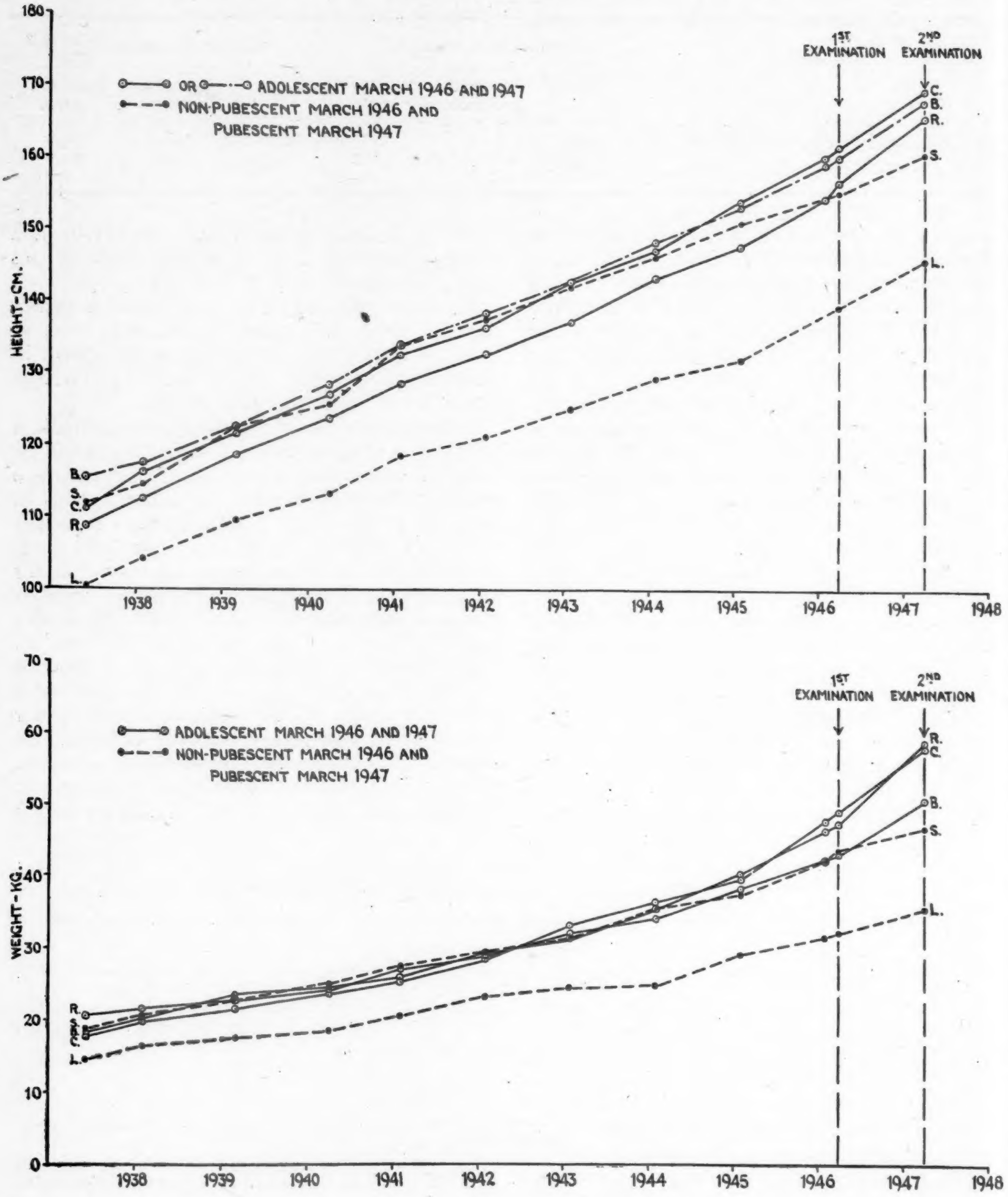
Although no quantitative comparison is drawn between height and weight increases in boys in different schools, the mean figures are shown in parallel to illustrate how far the same type of change is seen in each phase of development.

Comparison of results. In comparing the findings in the two schools (tables 1, 3, and 6), it will be seen that whilst there are general similarities, there are also certain apparent discrepancies. Thus in school A it was found that the increase in height in the boys reaching pubescence during the experimental period and those remaining pubescent for the whole year corresponded very closely, whereas in school B growth was more rapid in those who remained pubescent than in those who reached pubescence (7·44 cm. as compared with 6·35 cm.). In view of the small numbers of boys in Group I and II in school B, and the considerably larger groups which correspond in school A, it can be assumed that the samples in school A are more representative, and it has been shown that the difference observed in Groups I and II are not in

TABLE 6

GRADINGS OF SCHOOLS A AND B COMPARED

Grading	Height increment (cm.)	
	School A	School B
Non-pubescent-Non-pubescent ..	4·8; 4·3	4·51; 3·81 (two years preceding first grading as NP)
Non-pubescent-Pubescent	6·2; 6·1	6·35
Pubescent-Pubescent	6·0	7·44
Pubescent-Adolescent	8·9	10·29
Adolescent-Adolescent	8·3	7·14
	Weight increment (kg.)	
Non-pubescent-Non-pubescent ..	2·67; 2·80	1·81; 2·17 (two years preceding first grading as NP)
Non-pubescent-Pubescent	3·76; 4·75	5·77
Pubescent-Pubescent	4·65	6·94
Pubescent-Adolescent	7·12	10·32
Adolescent-Adolescent	9·19	8·51



Figs. 2 and 3.—Individual growth curves of five boys aged 15 years 1 month to 15 years 4 months in March, 1947, showing effect of early or late maturity.

fact significant (table 4). From this it would appear that an acceleration of growth occurs approximately six months before the appearance of clinical manifestations of pubescence, and continues with little change throughout the period of pubescence.

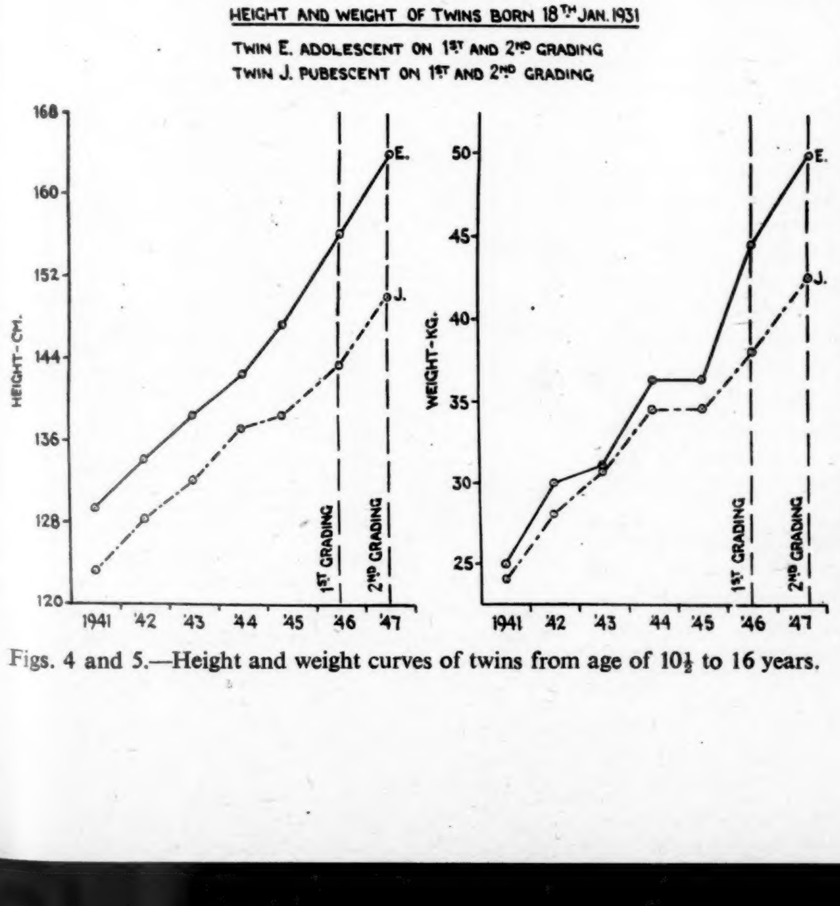
A further discrepancy is seen when boys attaining adolescence during the experimental period are compared with those who were adolescent on first examination. In school A the weight-gain was greatest in those who were already adolescent, whilst in school B it was greatest in those attaining adolescence. In this instance the groups compared were considerably larger in school B than in school A and more significance is attached to the school B findings. It is probable, however, that the apparent discrepancy may here be influenced by the age-range studied in the two schools. School B, containing boys up to 16½, would tend to have a larger proportion of boys in late adolescence than would school A, where the boys included in the analysis were all under 15. On this assumption, the discrepancy could be explained if the rapid acceleration of weight-gain associated with attainment of adolescence continued during the first year of adolescence, and then tended to decrease though still remaining greater than weight-gain during early pubescence. It is of interest in this connexion to note that the 'Brush Regular Series' of annual increment means for standing height and weight for boys, quoted by Simmons (1944), show in both instances a steep rise between 13 and 14 years, followed by a less steep fall between 14 and 15 years, and subsequently a more rapid fall between 15 and 17 years. This bears out the view that deceleration in height and weight gain is more rapid in later adolescence: though it suggests that the boys comprising the Brush series matured on the average rather earlier than those included in the present study.

Individual growth curves. The five boys remaining in school A, who were over 15 in March, 1946, were so closely matched in age (within three months) whilst showing different degrees of maturity, that their individual height and weight curves are shown over a ten-year period (figs. 2 and 3) in order to illustrate the effects of late and early development. The two boys (L and S) whose heights and weights are shown by a regularly broken line were non-pubescent in March, 1946, and pubescent in March, 1947. The remaining three boys, C, B, and R, were adolescent on first and final examination.

It will be seen that whilst the curves for both height and weight are closely similar or parallel to within fifteen months of the first examination, from that point there is a marked acceleration of increase in height of the earlier-maturing boys. A similar acceleration of weight-increase is seen in two of the boys (R and C) preceding and during the experimental period, whilst in the third of the earlier-maturing boys (B) it comes during the experimental period. The two late-maturing boys (S and L), whose first manifestations of pubescence appeared during the experimental period, also show a slight acceleration of growth associated with the onset of pubescence, but this is considerably less than that of the more mature boys.

These individual curves, therefore, bear out the general observations made on the analysis of the growth of maturity groups, viz. that the onset of puberty is associated with some acceleration of annual increase in height and weight, and that this acceleration becomes more rapid with the transit from pubescence to adolescence, continuing into the adolescent period. Whilst both height and weight are affected, the acceleration of weight-gain in early adolescence is the more marked.

Two further individual growth curves (figs. 4, 5) are



Figs. 4 and 5.—Height and weight curves of twins from age of 10½ to 16 years.

TABLE 7

ANALYSIS OF 662 EXAMINATIONS ON BASIS OF MATURITY AND AGE

Age group (years)	No.	Non-pubescent (per cent.)	Pubescent (per cent.)	Adolescent (per cent.)	Non-adolescent (per cent.)
9–10	52	100	0	0	100
10–11	40	95	5	0	100
11–12	74	86·5	13·5	0	100
12–13	95	64·2	35·8	0	100
13–14	135	47·4	43·7	8·9	91·1
14–15	120	12·5	39·2	48·3	51·7
15–16	78	1·3	29·5	69·2	30·8
16–17	33	6·1	18·2	75·7	24·3
17–18	35	0	11·4	88·6	11·4

included from school B. The two boys were twins (probably binovular), and had never been separated, so that dietetic and environmental factors had remained virtually identical. Twin E was graded as adolescent on examination in July, 1946, and March, 1947, and Twin J as pubescent on both occasions. It will be seen that whilst the later-maturing twin was smaller from the age of 10 (when the first measurements were available), the discrepancy between the two becomes very much more marked with the onset of puberty in Twin E. Thus Twin E shows a well-marked acceleration of increase in height and weight occurring approximately a year before a similar, but less striking, acceleration in the case of Twin J. (The curves suggest that acceleration of growth in height precedes that of increase in weight, but this point is obscured by the fact that both twins failed to gain weight in 1944-45.)

Onset and duration of pubescence. In the course of this investigation it was noted that a considerable number of boys were classified as pubescent on both first and final examination, and that this phase of development might therefore last at least a year. In order to obtain further information on this point, 561 examinations were made on boys aged 9 to 17 in the two residential schools, supplemented by 101 examinations of working boys aged 14 to 18 in two residential homes in Edinburgh. (Boys aged 18 to 19 were not included, owing to military service making the available samples unrepresentative.) An analysis of the 662 examinations shows the percentage of boys classified as non-pubescent, pubescent, adolescent, and non-adolescent (i.e 100 minus percentage adolescent) in each year of age (table 7, figs. 6 and 7).

The significance of these figures in relation to the effect of raising the school leaving age from 14 to 15 on the maturity of boys seeking employment has been discussed elsewhere (Ellis, 1947a, b). They are included here to illustrate the possible effect of late or early appearance of pubescence on the growth curve of individual boys. Thus if the percentage of non-pubescent and non-adolescent boys in each year of age is graphed as in fig. 7, the stippled area representing the period of pubescence, the figure indicates that boys reaching pubescence at 13·5 years will, on the average, remain pubescent for 1·2 years. For those reaching pubescence earlier or later, the period of pubescence will have a longer duration, approximately 2·5 years when the age is 10·5 and 2·4 years when the age is 14·5 years.

If, as is indicated above, each phase of development has a characteristic growth pattern associated

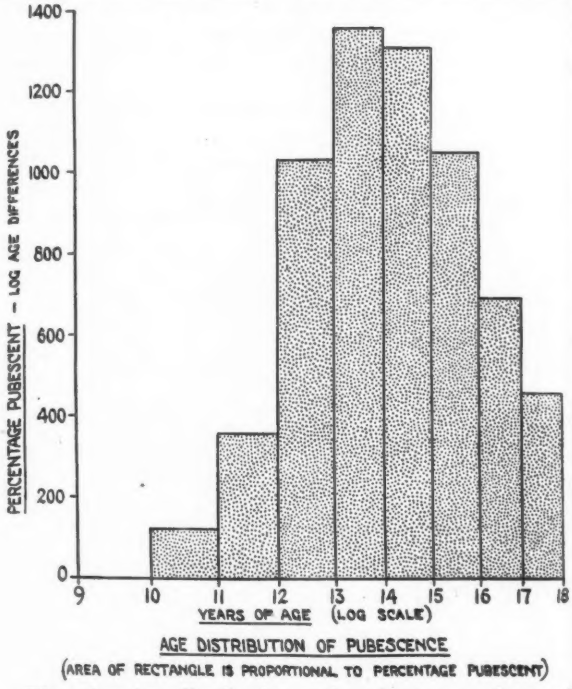


Fig. 6.—Age-distribution of pubescence. Area of rectangle is proportional to percentage pubescent in each year of age.

with it, early or late appearance of manifestations of pubescence might be expected to be associated with a prolonged period of ‘ pubescent growth ’, followed by the more rapid growth characteristic of transition to adolescence.

This is not contrary to the generally-accepted principle that children who mature early also tend to stop growing early. This will be clear if it is remembered that pubescence does not represent ‘ maturity ’ or necessarily correspond with spermatogenesis in boys or menstruation plus ovulation in girls. In fact fig. 7 indicates that a boy who shows manifestations of pubescence at 10·5 years is still likely to reach adolescence 1·7 years earlier than a boy whose age-onset of pubescence is 13·5 years, despite the longer pubescence of the earlier-maturing boy.

The actual duration of pubescence in relation to age-onset of its appearance, has received little attention in the majority of growth studies on boys. Richey (1937) states that in over 90 per cent. of boys showing pubic hair at one birthday, axillary hair (his criterion of attainment of adolescence) was present at the next, and he assumed that this would in fact be the case in boys who were not available for re-examination. In the present study it will be seen that of twenty-five boys in school A graded as pubescent on first examination, sixteen (72 per cent.) were graded as pubescent a year later. It is probably significant that the average age of these sixteen boys was 12 years 10 months at first examination, and that that of the remaining nine who became adolescent in the interim was 13 years 5 months. The criteria employed for grading as pubescent or adolescent in the present study were not of course the same as Richey's, and any study of duration of pubescence would have to take into account other signs than presence of body hair.

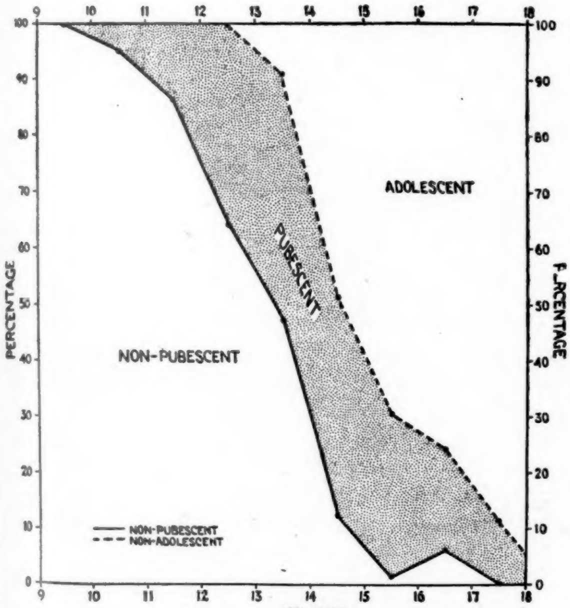


Fig. 7.—Percentage of non-pubescent and non-adolescent boys in each year of age, showing duration of pubescence.

Summary and Conclusions

1. An investigation of growth over a twelve-month period was carried out on 154 boys who were aged 12 to 16½ years at the conclusion of the period of observation. The boys were derived from two residential schools. They were graded as non-pubescent, pubescent, and adolescent at the beginning of the experimental period, and on the basis of subsequent grading were classified into the following groups: (1) those who remained non-pubescent throughout; (2) non-pubescent becoming pubescent during the experimental period; (3) those remaining pubescent throughout; (4) pubescent becoming adolescent; and (5) those adolescent throughout. The mean values for increase in height and weight, and for leg-length in the case of boys in one school, were determined for each of these groups. Comparisons were made only between boys resident in the same school.

2. Although the findings in the two schools were not consistent in every particular, there was clear evidence of: (1) an acceleration of both height and weight increment preceding the clinical manifestations of pubescence, and continuing through the period of pubescence; and (2) a more rapid gain in both height and weight associated with the attainment of adolescence, and continuing into early adolescence; (3) subsequent deceleration in height increment noted in the older group of adolescents.

3. The effect of early or late maturity is illustrated by individual growth curves. Since the age-range of onset of pubescence and of adolescence may show a variation of several years in different individuals, it is emphasized that composite growth curves based on chronological age will tend to smooth out these characteristic patterns which depend on physiological rather than on chronological age. This has a practical application when individual growth curves are compared with composite curves, and also when comparison is made between age-groups of mixed maturity in different countries or of different nutritional status. The introduction into routine medical examinations of some simple standard of maturity-grading such as that suggested would make it possible to compare groups of the same age and of approximately the same degree of

maturity. It would also make it possible to determine whether differences in climate, nutrition etc., influence the average age of onset of puberty, and hence the percentage of boys in each maturity-grade in each year of age.

4. Evidence is adduced that the duration of pubescence may vary considerably in different individuals, and is probably longest in those reaching pubescence early or late, and shortest in those in whom clinical manifestations of pubescence appear at 13·5 years.

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ETIOLOGICAL ASPECTS OF GASTRO-ENTERITIS*

BY

E. HINDEN, M.D., M.R.C.P.

The group of diseases known officially as 'diarrhoea and enteritis under two years of age' is one of the major hazards which menace the life of the young infant. The group consists of several seemingly distinct clinical entities; one of these, known from its incidence as 'epidemic diarrhoea of the newborn' has recently attracted much attention—to a degree out of proportion to its importance as a killing disease. For indeed the as yet undifferentiated remainder, less severe but more widespread, cause a much greater loss of life. The etiology of these diseases, and their relationship within the group, are not yet fully determined; the object of this study is to help elucidate these two problems.

Gastro-enteritis, to use a non-specific name for all the intestinal disorders, was particularly severe in the district of North Kensington, a part of the Royal Borough of Kensington, during the years 1938-39-40 (table 1). Kensington had the highest gastro-enteritis mortality rate in 1938 of all the Metropolitan Boroughs, and was second in 1937 and 1939. Correspondingly, the total infant mortality rate was also high, the borough being worst on the list in 1937 and 1939. The figures show that this was due mainly, but not entirely, to the high death rate from enteritis.

TABLE 1

TOTAL INFANT MORTALITY UNDER ONE YEAR AND GASTRO-ENTERITIS MORTALITY UNDER TWO YEARS, FOR ENGLAND AND WALES, AND THE BOROUGH OF KENSINGTON: RATES PER 1,000 LIVE BIRTHS. (REGISTRAR-GENERAL, 1938d)

		1937	1938	1939	1940
England and Wales	total mortality	58	53	50	56
Kensington		83	78	64	58
England and Wales	gastro-enteritis mortality	5·5	5·3	4·7	4·8
Kensington		19·8	24·6	12·9	10·9

The relative importance of gastro-enteritis as a killing disease of infancy has increased of late. The death rate for the ordinary infectious diseases of infancy, and for tuberculosis, have both fallen steadily during the past ten years to about half their former value; but the death rate for "enteritis and diarrhoea" has fallen only a little. Gale (1945) in his discussion of the secular trends of disease in childhood, points out that until 1921 the fatality from this disease was decreasing rapidly, but that since that date it has remained stationary, even though total infant mortality has continued to fall (table 2). A similar phenomenon has been noticed in America, where Frant and Abramson (1944) stress that while deaths due to diarrhoea in the age groups one to twelve months have fallen in the years 1926-1939, those in the first month of life have actually risen. The English figures show that gastro-enteritis alone is responsible for about 10 per cent. of the total infant mortality. But, of this total, nearly half is due to causes which operate before the baby is well and truly launched into the world. Such are prematurity and congenital deformities, and the mortality due to them is given in line 4 of table 2. The mortality due to birth injury, approximately 2·5 per thousand, should also be added to this. What is left is the mortality sustained by healthy, normally-born babies, and of this, gastro-enteritis is responsible for about 16 per cent. It is surpassed in importance as a killing disease only by pneumonia. During the three bad years in Kensington, although no outbreak of diarrhoea neonatorum was encountered, enteritis was responsible for eighty-one out of the 120 deaths under one year that took place in the County Hospital; pneumonia caused twenty-three, and all other conditions but sixteen.

Clinical Material

The clinical material to be considered consists of all cases of gastro-enteritis treated in the County Hospital during the twenty-four months from April 1, 1938, to March 31, 1940. There were 148 such, of whom sixty-five died and eighty-three recovered—a case-mortality of 44 per cent. An additional twenty fatal cases are included in the discussion of aspects of etiology other than case-mortality; ten were admitted between January and March, 1938; and another seven, admitted during 1937, also died within these three months; three more died in the period April to December, 1940.

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* Based on a thesis for the M.D. degree of the University of Cambridge.

TABLE 2

INFANT MORTALITY (DEATHS UNDER ONE YEAR PER 1,000 LIVE BIRTHS) FROM CERTAIN CAUSES: 1931-40 (REGISTRAR-GENERAL 1940)

	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940
All causes	66	65	64	59	57	59	58	53	50	56
Various infections other than tuberculosis	5·0	5·2	4·5	4·0	3·1	3·9	3·2	2·4	2·3	2·8
Tuberculosis	1·04	1·00	0·82	0·68	0·55	0·59	0·63	0·60	0·51	0·59
Enteritis and diarrhoea	5·4	6·2	6·4	5·0	5·3	5·6	5·3	5·1	4·3	4·4
Developmental and wasting diseases	28·3	28·3	29·1	27·6	27·1	26·8	26·9	24·9	24·7	25·0
Remainder	26·6	24·4	23·0	21·3	20·9	21·7	21·6	19·7	18·6	23·1

This makes a total of eighty-five fatalities, which is the number of deaths from gastro-enteritis during the three years 1938-39-40.

Case Mortality and Seasonal Incidence

This disease notoriously carries a heavy case-mortality; taking together the figures given in six recent studies in this country, the average case-mortality is one in three (table 3).

TABLE 3

CASE-MORTALITY OF GASTRO-ENTERITIS

Author	Total cases	Deaths	Case-mortality per cent.
Smellie (1939)	500	240	48
Campbell and Cunningham (1941)	574	159	27·7
Field et al. (1943)	100	23	23
Gunn (1944)	411	88	21·4
Alexander and Eiser (1944)	140	8	5·7
Gairdner (1945)	216	109	50
Total	1,941	627	32·3
This series	148	65	44

The distribution by age and sex of patients dying of the disease in England and Wales, and of the present series, is given in table 4. It will be seen (country-wide figures) that the incidence is fairly uniform over the first six months, being highest at about three months; it falls sharply after the end of the first year. This agrees well with the present series, and with the figures given by individual authors. Thus Gunn (1944) found that the age-group three to six months contained the largest number of cases (125 out of 411), and suffered also the highest case mortality, 30·4 per cent. The case mortality of the present series is: below three months, 60 per cent.; three to six months, 55 per cent.; six to nine months, 32 per cent.; nine to twelve months, 44 per cent.; one to two years, 15 per cent. The mean age of the fatal cases was 4·9 months; 70 per cent. of deaths occurred before six months of age, and only 5 per cent. after one year.

At all ages, baby boys suffer more than baby girls (4,321 boys and 3,677 girls), and the excess of male deaths is far more than would be expected on random sampling.

The seasonal incidence both for the country as a whole and in this series, is shown in table 5. Looking at the country-wide figures for the individual years, it is seen that December is one of the worst three months in every year, and January is so twice; these two months have the worst averages also. More detailed analysis (χ^2 test) shows that the high figures given by these months are unlikely to have arisen by random sampling, while the variations between the other months are of no significance.

This high winter incidence is all the more striking when it is recalled that formerly this disease was called ' summer diarrhoea.' Writing on this point, Gale (1945) says: ' The cause of this summer diarrhoea of infants is unknown, but from its epidemiological history it looks almost as though a disease had disappeared in the last war, except for a dying spurt of activity in 1921, and that the infantile diarrhoea of the present day, with its steady death rate and its higher incidence in winter may have a different causation.'

Other investigators also have noticed that the former high summer incidence is not found nowadays. Gairdner (1945) and Smellie (1939) both found that there was no particular seasonal incidence in their series, the latter explicitly remarking that ' summer diarrhoea is over.' On the other hand, Campbell and Cunningham (1941) found more cases in summer and autumn than in winter.

Consideration of the figures of the present series of cases shows that the incidence of the disease was highly irregular. There were three waves of high incidence: May, June, and July, 1938; November and December, 1938 and January, 1939; and February, 1940. The overall monthly average for the period was 6·2 cases; for the seven worst months it was nearly 12, and for the remaining seventeen months it was 3·8. ' Summer diarrhoea ' was conspicuously absent.

The Outbreak of War

It is interesting to examine the number of deaths in the borough in the months after the outbreak of war. The early winter rise in deaths did not occur; February suffered a heavy epidemic, and thereafter

TABLE 4

DEATHS DUE TO GASTRO-ENTERITIS, BY AGE AND SEX: ENGLAND AND WALES (REGISTRAR GENERAL 1938a), AND THIS SERIES

	Under 4 weeks	4 weeks 3 months	3–6 months	6–12 months	1–2 years	Totals
1938 : males	153	535	638	511	156	1,993
females	94	284	425	380	119	1,302
1939 : males	138	433	523	423	117	1,634
females	101	274	376	311	116	1,178
1940 : males	201	503	488	367	135	1,694
females	142	342	341	271	101	1,197
Total : males	492	1,471	1,649	1,301	408	5,321
females	337	900	1,142	962	336	3,677
This series : males females	2	20	38	21	4	56 29

the disease almost disappeared. This may be compared with the movement of the population: expectant mothers, and infants, were evacuated after the declaration of war, but as London did not sustain the expected bombing they trickled back as the winter passed. Yet the population fluctuations were nothing like as great as would be required to explain the fall in incidence on a simple per capita basis. The summer months were quiet; heavy bombing started in the autumn of 1940, causing the second wave of emigrations from London; and with this the winter of 1940-41 was very free from this disease.

Influence of Breast Feeding

The influence of breast feeding on gastro-enteritis has been noticed by several writers; it lessens both incidence and case mortality. Thus Robinson (1940) found that diarrhoea occurred in eighty of 171 artificially fed babies, but in only six of thirty-seven infants on the breast; the discrepancy is significant ($P<0\cdot01$). Ebbs and Mulligan (1942) considering 314 cases of gastro-enteritis, found that only seven (2·2 per cent.) were wholly breast-fed, and seventy-nine (25·2 per cent.) partly breast-fed; while in the general population 35·6 per cent. were wholly breast-fed, and 36·2 per cent. partly so. This is a considerable lowering of the incidences, and the differences are significant. Smellie (1939), Campbell and Cunningham (1941), Alexander and Eiser (1944), Gairdner (1945), and Weihl et al. (1947) also report a low incidence of this disease in breast-fed babies, but their figures do not include the proportion of breast-fed babies in the general population. With regard to mortality, Gunn (1944) found that the disease was not only less frequent, but also milder in the breast-fed, and Ormiston (1941) agrees that fewer breast-fed babies die of this disease. Ebbs and Mulligan (1943) curiously enough find a higher mortality among the breast-fed, possibly because the milder cases among the breast-fed babies were not admitted to hospital. The other writers mentioned above find the case mortality of the breast-fed about half that of the bottle-fed babies. Two further experiences may be quoted. Sakula (1943), describing an epidemic in a maternity nursery, found that, of eighteen infants who contracted the disease, fifteen died, all of them artificially reared. Cron et al. (1940), dealing with a similar attack in America, found eighteen deaths in twenty-two cases; here again, only the bottle-fed babies died; all the breast-fed babies recovered. Most writers agree that even a few weeks' breast-feeding improves the prognosis, even though the baby may be long off the breast when he falls ill.

There are, however, two recorded opinions differing from this view. Rice et al. (1937), writing of 'epidemic diarrhoea of the newborn,' state that breast-fed babies were as prone to infection as the others; and Lyon and Folsom (1941), describing a particular outbreak, found that the majority of the babies were breast-fed.

In the series under review, the information about breast-feeding is unfortunately far from complete. Of the eighty-five who died, thirteen were breast-fed up to their death, and another thirteen had been breast-fed for at least six weeks; the others had not been breast-fed for more than a short time. It appears that over 30 per cent. of the infants who succumbed had been breast-fed for six weeks or more—a period commonly considered to give a good resistance to this disease. Breast feeding did not afford the expected high protection against the virulent form of gastro-enteritis prevailing in the neighbourhood during those years. The data on the incidence of breast feeding among the recovered infants are too scanty to be of value.

TABLE 5

MONTHLY INCIDENCE OF GASTRO-ENTERITIS IN 1938–39–40 (REGISTRAR-GENERAL 1938b)*

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1938	498	429	374	319	344	335	450	481	422	459†	441†	490†
1939	348	274	308	315	257	311	293	279	226	264	277	414
1940	380	347	339	289	330	367	354	394	417	404	375	416
Average	409	350	340	308	310	338	366	385	355	376	331	440
Monthly incidence of 148 cases of gastro-enteritis (this series)												
1938				4	11	8	12	1	3	4	10	19
1939	11	5	2	6	4	6	2	–	4	7	2	3
1940	7	12	5									
Average	9	8·5	3·5	5	7·5	7	7	0·5	3·5	5·5	6	11

*** Note: This disease is NOT "diarrhoea and enteritis under two years", but "diarrhoea and enteritis other than colitis, not due to intestinal ulceration." The great majority of this group, however, is diarrhœa and enteritis under two years.)**

† Figures are for 1937.

Urban and Rural Areas

Gastro-enteritis is predominantly a disease of the urban community; it falls much less heavily on the inhabitants of the countryside (table 6). It will be seen that the death rate falls with the density of the population; Gairdner (1944) also draws attention to this fact. The same trend for neonatal mortality has recently been reported from Scotland (Department of Health for Scotland, 1947). Another curious fact shown by the table is the high death rate among illegitimate children in all areas, and particularly in Greater London.

TABLE 6

DEATHS FROM GASTRO-ENTERITIS UNDER ONE YEAR AS A RATE PER 1,000 LIVE BIRTHS, IN VARIOUS PARTS OF THE COUNTRY, 1938. (REGISTRAR-GENERAL, 1938c).*

		All deaths	Legitimate children	Illegitimate children
England and Wales	males	5·77	5·46	12·75
	females	3·91	3·67	9·31
	persons	4·86	4·59	11·07
Greater London		8·72	7·93	24·48
County Boroughs		5·68	5·49	9·73
Other urban districts ..		3·01	2·90	5·68
Total for all urban districts		5·44	5·13	12·43
Rural districts		2·15	2·04	4·59

***Publication of this table was suspended for the years 1939 and 1940.**

Hospital Infection

There remains one other important etiological factor, hospital infection. Paterson (1944) says, 'Debilitated infants contracting the disease in hospital show a much higher mortality than healthy infants contracting it at home'; and other writers also stress the dangers of hospital infection. Field et al. (1943) found fifteen deaths among forty-six hospital-contracted infections, as against eight among fifty-four home contracted ones—a significant difference, though Campbell and Cunningham (1941) failed to find any difference. Gairdner (1945) makes the important observation that gastro-enteritis occurring in a 'recently discharged' infant should really be considered as hospital-contracted. Hospital gastro-enteritis is extremely infectious (Ormiston, 1941; Gunn, 1944), and it is likely that some at least of the notorious relapses of this disease are due to reinfection. Alexander and Eiser (1944) state that, among seventy-three cases nursed in individual cells, there were six relapses and one death; while among sixty-seven nursed in a big ward, under the rigorous bed-isolation regime of a fever hospital, there were twenty-one relapses and five deaths, a highly significant finding.

Of the present series of 148 cases, eighty-eight infants were admitted with gastro-enteritis, and twenty-seven of these died, a case mortality of 31 per cent. There were sixty infants who contracted the disease in hospital, and of them thirty-eight died (63 per cent.). This is a very large difference. But in addition, there were nine infants (of whom four died) who contracted the disease within four days of leaving hospital, and who probably were infected there, and another eight infants (of whom four died) whose clinical history strongly suggests that they had recovered from the enteral infection with which they were admitted, only to contract another infection while in hospital. Making these adjustments, there were seventy-seven infants acquiring gastro-enteritis in hospital, of whom forty-six died (a case mortality of 60 per cent.; and seventy-nine who contracted the disease at home, of whom nineteen died (24 per cent.).

Hospital infection is more than twice as deadly as home infection; it was responsible for 49 per cent. of the cases, and for over 70 per cent. of the deaths. The diagram shows the distribution of these cases by months, according to whether the infection was contracted in hospital (above the line) or outside (below the line); the deaths are shown hatched. It shows the pronounced epidemic character of the hospital outbreaks as compared with the much steadier incidence of the outside cases.

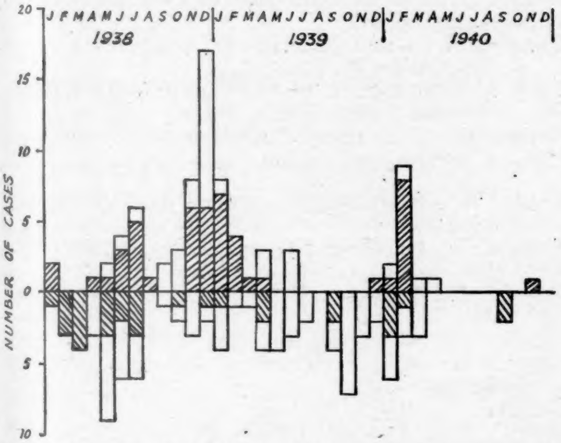

FIG.—Monthly distribution of cases of gastro-enteritis; infection contracted in hospital shown above the line, outside cases below the line. Fatal cases are shown hatched.

Discussion

Three salient factors emerge from this study. The first is the seasonal incidence. The old 'summer diarrhoea' was a food-conveyed disease, with flies an important vector: naturally such a disease would have its greatest incidence in the warm months. But with improvements in hygiene, the withdrawal of horsed traffic from the towns, a rising standard of living, and better management of infant feeding by the public, this disease has virtually disappeared. It is possible that present-day enteritis is a new disease; more likely it has been slaying its tens all the time, though overshadowed by 'summer diarrhoea' slaying its hundreds. Were it also food-carried, it should have disappeared with its prototype. But it has not; and it is associated not with high summer, but with the season of coughs and sneezes. The close association between present day gastro-enteritis and respiratory infections is commented on by all authors; in one paper (Frant and Abramson, 1939), it is actually called 'upper respiratory diarrhoea'. There is a suggestion here that the noxious agent gains access to the infant through the respiratory channels.

The second is the beneficial effects of breast feeding. This is easy to understand: breast-milk is not liable to the same contamination as artificially-prepared food, and, having a weaker buffering power than cows' milk, does not destroy the protective barrier of the gastric acidity. But these explanations do not cover the puzzling fact that a few weeks' breast feeding give protection even subsequently, when the baby is bottle-fed and therefore presumably at risk. They also do not explain why, in the two outbreaks of neonatal diarrhoea mentioned above, breast feeding afforded no protection. It is tempting to assume the presence of protective substances in breast-milk; this would explain both these discrepancies, but direct attempts to demonstrate such substances have failed.

The third important factor brought out is the higher mortality in towns. General sanitation and water supplies are better in the towns, the fly nuisance is less, and medical facilities are easier to obtain; nevertheless the disease is more deadly in the towns than in the countryside. One possible explanation is that rural mothers are more likely to breast-feed their nurslings than are urban mothers; but it is unlikely that this could account for the very big difference between Greater London and the County Boroughs. Another explanation is that the danger from gastro-enteritis increases with the concentration of susceptibles at risk, that is, roughly with the density of the population. This is known to be of great importance in determining the spread of other infectious diseases, such as measles; and it is interesting to note that the expected waves of measles epidemics did not occur after the evacuation of children from the densely populated cities, just as the expected winter epidemic of gastro-enteritis did not occur in Kensington in 1939-40.

The greatest concentration of susceptibles, of course, is found in the children's wards of hospitals, and it is here that the greatest infectivity and mortality are found. Other factors have to be appraised when considering hospital infectivity. The first is the enfeebled condition of the inmates, who presumably are not in good health. This factor has weight: it is shown later that one particular class of hospital admission, the infant who has done badly from birth, and is admitted because he is not getting on, rarely recovers from gastro-enteritis. But its importance should not be overstressed: with the above exception, it was found that the primary disease which secured entry of the infant to hospital is without effect upon the outcome of the enteritis, and it is common knowledge that hospital infections light on healthy nurslings admitted because of maternal disease and upon surgical cases in good general health. Another consideration is that the disease may be spread by faulty feeding technique. This view is taken by Stern (1947), who blames the milk-film which is left on the inside of the feeding bottle. But it is unlikely that this can be the whole explanation. High infectivity was found even with the strict barrier technique of a fever hospital; and while outbreaks of 'non specific gastro-enteritis' are common, those of proven food-conveyed disease (Salmonella and Shigella infections) are much rarer. Only one such outbreak occurred during the three years in the present series (Hinden, 1940). It is possible, too, that the virulence of the noxious agent may be heightened by passage.

There are probably two main factors concerned in the high death rate among illegitimate babies: the low incidence of breast-feeding, and the high proportion of them nursed in institutions.

The striking divergences between the published case mortalities (table 3) demand further attention. How was it that in North-West London only eight infants died out of 140, while in West Middlesex 109 were lost out of 216? Such differences are commonplace in any compilation of case mortalities. It is out of the question that these divergences should have arisen by mere chance: the material cannot be homogeneous, the cases are not comparable. It seems indisputable that ' gastro-enteritis ' is not a single disease; there is a mild type, probably again heterogeneous, and a severe type, epidemic in character, which prevails in different places at different times. It is this second type which causes most of the deaths, and it is this disease, occurring in many small localized epidemics during the winter, which is responsible for the heavy winter mortality. The evidence indicates that this disease was rampant in Kensington in 1937-39, in West Middlesex in 1944-45, and in Liverpool in 1945-46. It is by no means coincidence that Sakula's (1943) report of an outbreak with a case mortality of over 80 per cent. also came from Middlesex. The figures for Liverpool are instructive: from July, 1945, to June, 1946, this city had 17,294 births and 330 deaths from enteritis; during the same period, London had 52,597 births and 320 deaths (Registrar-General, 1945-46). Liverpool had less than one-third the births of London, but more deaths, giving a death rate three times as large (the death rate is actually 19·1 per thousand, the same as Kensington in 1937). Small epidemics of this serious disease catch the public eye from time to time, as recently at Leicester and Preston, and during last summer on the U.S. Army Transport *Zebulon B. Vance*, carrying war brides and babies to the U.S.A. On this voyage, nineteen infants contracted the disease, and nine died. (Bulletin of U.S. Army Medical Department, 1946.) It is this disease, epidemic in concentrations of susceptible infants in the winter months, associated with respiratory infection, which kills 3,000 infants each year. There is as yet no method of differentiating it from other forms of gastro-enteritis, though it may be connected with the distinction between ' dehydrated ' and ' non-dehydrated ' cases made by most observers. Nevertheless, it is possible that in the future this illness may be as clearly distinguished from other intestinal disorders, as is typhus fever from typhoid fever to-day.

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ETIOLOGICAL ASPECTS OF GASTRO-ENTERITIS

PART II

BY

E. HINDEN, M.D., M.R.C.P.

Classification of enteritis presents many difficulties. On this subject, Paterson (1933a) said, 'The more one studies the problem of the diarrhoeal disease of infancy, the more complicated it appears'; this same writer (1944) divides gastro-enteritis into three main groups: infective, dietetic, and symptomatic. The first group, which is better called specific, is due to an infection by a known pathogen, such as the Gram-negative bacilli of the coli-typhoid-dysentery group. A sub-group of this is the diarrhoea caused by specific infection of other abdominal organs, such as pelvic peritonitis or tuberculous mesenteric adenitis. The second group is due to gross errors in feeding, and is becoming less common nowadays, as correct knowledge of infant feeding extends through the community. The third group, the commonest, is thought to be due to infection in the body outside the abdomen; this is the 'parenteral type.' Campbell and Cunningham (1941) prefer to call this last group 'alimentary-infectious complex, with or without parenteral infection.' This latter name, though vague, seems better than 'parenteral diarrhoea' in that it recognizes the existence of infection directly influencing the alimentary system and places parenteral infection as a concomitant, rather than a causative disorder.

In this series, ten infants only, out of the total of 148 were suffering from gross dietetic errors; seven recovered and three died. There were but two cases in the 'specific infection' group: one was suffering from a Salmonella infection, the other from B. dysenteriae Sonne. Each of these had another infection (one respiratory, one dermatitis) and were classed as 'parenteral' on admission. Two infants who presented as frank dysentery, and eleven who were involved in a small S. aetrycke outbreak (Hinden, 1940) have not been included. It will be seen that the bulk of the patients—136 out of 148—were suffering from 'alimentary infectious' diarrhoea, and of these sixty-six, roughly half, had some form of parenteral infection. These figures will be more fully discussed later, when the relation of parenteral infection to diarrhoea is dealt with. Advances in classification will come through splitting off specific types of illness from this 'omnibus' group.

Route of Invasion

Accepting, then, that there is infection, enteral or parenteral, what is the route of invasion? The mouth suggests itself; but the utmost care in sterilizing feeds and feeding apparatus does not limit an epidemic. Felsen and Wolarsky (1942) concluded that 'The mode of transfer is from "mouth-to-mouth," rather than from "intestine-to-mouth" as is the case with the primary enteric pathogens.' It is noteworthy, too, that wholly breast-fed infants do contract this disease, albeit in small numbers. Feibush (1945) described an epidemic of enteritis in New York, which was highly infectious and attacked individuals of all ages. The onset of the disease was regularly preceded by a sore throat, and the author expresses his opinion that the respiratory channels were the route of entry. This is not the gastro-enteritis of infancy, but it may be a near relative.

Bacteriology

The bacteriology of this disease has been intensively studied, and a bewildering array of pathogens suggested. The noxious agents implicated fall into three groups, the Gram-negative bacilli, other bacteria, and viruses. In the first group, the known pathogens, the food-poisoning (Salmonella) and dysentery (Shigella) families have to be considered; but they are common in warm climates. Ouyang (1940) reported from China that he found a pathogen (usually Shigella) in 63 per cent. of 190 cases; Moore and Dennis (1940) in the Lebanon isolated a pathogen (bacterial or protozoal) in 50 per cent. of cases under one year old, and in 66 per cent. under two years old; in nearby Palestine Meyer (1943) considered that half his cases of summer diarrhoea were due to Shigella infections; in Montevideo Hormaeche et al. (1943) analysed 668 cases of enteritis, and found Shigella responsible for 39 per cent. of cases, Salmonella for 23 per cent.; and in a recent study from Ohio, Weihl et al. (1947) reported finding a dysentery organism in 18·5 per cent. of 221 cases.

In temperate climates, however, it is rare to isolate a pathogen. Bloch (1941) writing of diarrhoeal diseases in Glasgow, found that of 908 dysenteries, only 3·3 per cent. were under one year of age; paratyphoid and typhoid fevers also were uncommon in this age-group. Evans (1942) found that most of the cases of hospital diarrhoea in older children and adults were due to known pathogens, but it was not so with the young children; and no pathogen was isolated from any of his six fatal cases. Crowley et al. (1941) found no evidence of abnormal organisms, of soluble toxins, or of poisons formed in the maternal breast. Abt and Abt (1944) agree with Bloch (1941) that enteric fevers are rare in childhood, but Neter and Clark (1944b) write, 'the importance of paratyphoid bacilli as incitants of diarrhoeal disease in infants and children is stressed.' Considering other Salmonella organisms, Neter (1944) reports some sporadic outbreaks due to S. typhi murium and Abramson et al. (1939) describe four cases in neonates.

There is evidence that occasionally the physiological commensals of the coli groups are concerned in the pathogenesis of this disease. Blacklock et al. (1937) pointed out that normally B. coli is absent from the upper bowel, but that it invaded this region in parenteral infections, and was found most frequently in primary gastro-enteritis. This may be related to the diminished gastric and enteric secretions found in such infections. But their work does not decide whether the presence of B. coli in this unusual situation causes the enteritis, or results from it. The theory that infantile gastro-enteritis is due to an 'endogenous' infection is an attractive one, and is supported by Marriott (1944) and Cruickshank (1945, 1946); but it does not account for the extreme infectivity of the disease. The paracolon bacilli are in a slightly different category; they are only occasionally found in the normal individual, and their significance is still obscure. Anderson and Nelson (1944) isolated a para-aerogenes paracolon bacillus in one epidemic, but are doubtful whether it was of etiological importance. McClure (1943), describing four outbreaks of epidemic neonatal diarrhoea, writes, 'Haemolytic colon organisms show a much greater incidence in infants with epidemic diarrhoea than in well infants in the same nursery.' He tried to reproduce the disease experimentally in cats, but with inconclusive results. Neter and Clark (1944a) sum up, 'The role played by paracolon bacilli in diarrhoeal diseases remains obscure.'

Other bacteria also have been accused of causing gastro-enteritis. Neter and Farrar (1943) discuss the importance of Proteus vulgaris and P. morgani, but come to no definite conclusion; Walcher (1946) isolated B. mucosus capsulatus (Friedländer's group) from a small epidemic in a babies' home; Staph. aureus has been blamed in the U.S.A. by Felsen and Wolarsky (1942), and in Australia by Draper and Brown (1946); Sakula (1943) blames Ps. pyocyanea for the epidemic he describes, and Cron et al. (1940) report an epidemic caused by a haemolytic streptococcus.

It seems, then, that many organisms are occasionally responsible for an outbreak of gastro-enteritis, but Fothergill (1944) sums up by saying, 'In spite of such researches, there remain a large number of instances of summer diarrhoea in which the etiology is obscure.'

Possibility of Virus Causation

The possibility that gastro-enteritis of infants, and especially of neonates, may be due to a virus has been discussed many times. Campbell and Cunningham (1941) consider that a virus might be the cause of some at least of their 'alimentary-infectious' group. Both Crowley et al. (1941) and Bloch (1941) consider that the epidemics they describe were due to viruses. It is interesting that in this latter epidemic, onset was usually with rhinitis. Lyon and Folsom (1941) discuss 'epidemic diarrhoea of the newborn,' and, after excluding all cases with general sepsis, obvious systemic disease, and bacillary dysentery, consider the others to be due to a virus, possibly akin to the influenza virus. They discovered the interesting fact that citrated whole blood from convalescing influenza patients was markedly effective in treatment, while ordinary blood was useless. They also point out that the conception of 'parenteral diarrhoea' only became current after the great influenza pandemic, and speculate whether this disorder is not merely the form taken by influenza in the very young. Gunn (1944a) also considers that an influenza-like virus might be an important pathogen in gastro-enteritis. Dr. G. B. Ludlam (Dept. of Health for Scotland, 1947) gives a more recent opinion: 'A virus has been implicated in several epidemics, but the etiology of this condition cannot be regarded as settled.'

Viral diarrhoea in adults has attracted much attention of recent years, on both sides of the Atlantic. Typical descriptions have been given by Brown et al. (1945) in this country and by Feibush (1945) in New York. Discussing this disease, Reimann (1944) writes, 'It is unknown at present whether or not the disease is related to the severe epidemic diarrhoeal disease of unknown cause which affects new-born infants in nurseries.' A good account of the clinical features is given by Reimann, Hodges, and Price (1945) and of the bacteriology by Reimann, Price, and Hodges (1945); they conclude, 'These results . . . suggest that the causative agent of the disease is filtrable, airborne, enters through the respiratory tract, and is present in the oropharynx and stool but not in the blood.'

These last authors produce good evidence of the viral nature of adult epidemic diarrhoea. There is also direct evidence implicating a virus in infantile gastro-enteritis. Light and Hodes (1943), after vainly attempting to infect the usual small laboratory animals, finally succeeded with calves. Here are their conclusions:

'1. In connexion with four separate epidemics of diarrhoea of the newborn, a filter-passing agent has been isolated which regularly produces diarrhoea in calves.

'2. In the attempts so far made, this agent has not been isolated from the stools of normal infants or normal calves.

'3. The evidence suggests, though it is not conclusive, that the agent may be a cause of epidemic diarrhoea of the newborn.'

In 1944, Buddingh and Dodd described an epidemic of diarrhoea associated with stomatitis. From all forty-five sore mouths tested, and from all twelve bad stools examined, a virus was extracted which produced keratitis in experimental animals. The high infectivity of this diarrhoea, and the clinical description they furnish, are indistinguishable from those associated with hospital epidemic diarrhoea. They make the interesting point that adults may be, or become through contact, temporary carriers of the virus. Evans (1942) dealing with hospital diarrhoea, noticed that during the attacks of non-specific diarrhoea in young infants, there were always coughs and colds about in the ward, often only in the older children who did not suffer from diarrhoea. Buddingh (1946) has since found this virus in ten epidemics of neonatal diarrhoea. On balance, there seems to be at least as much evidence indicating a viral cause, as a bacterial, in gastro-enteritis of temperate climates.

Pathology

The pathological changes found post-mortem have been described by several of the writers already cited. The most nearly constant lesions have been found in the intestine, regional lymph glands, and the liver. The mucous membrane of the intestine has shown all changes from a mild congestion to active ulceration; both the mesenteric glands and Peyer's patches have been found swollen and hyperaemic. Parenchymatous degeneration of the liver is very common; this toxic change has also been noted in the kidneys and heart. Acute oedema of the brain, at times with haemorrhages and with flattening of the convolutions, has also been reported. The findings point to an acute infection falling on the intestine followed by spread along the intestinal lymphatic and vascular channels. Sakula (1943) however, considered that his patients died of acute toxaemia, rather than of intestinal infection. Morbid changes in other organs are usually found: pneumonia, otitis, and mastoiditis.

In the present series, twenty-two autopsies were performed. In nine of them no gross changes were found; in the other thirteen there were naked-eye morbid changes (microscopic examinations were but rarely carried out). In ten cases the intestine was found affected: the degree varied from thinning and ballooning of the small intestine to ulceration and necrosis of the mucous membrane. Fatty change in the liver was observed five times; inflammation of the regional lymph-glands four times. Rarer changes were congestion of spleen and cloudy swelling of kidney, necrosis of wall of gallbladder, and a peritonitis due to B. coli and Ps. pyocyanea. Here again, the evidence points to the brunt of the infection falling on the intestine, and spreading thence by the lymphatic and portal circulations.

'Parenteral Infection'

The problem of the relationship of 'parenteral infection' to infantile diarrhoea is an important and a difficult one. The observation that infants suffering from diarrhoea also frequently suffer from an infection outside the alimentary canal (such as pneumonia, otitis media and mastoiditis, and septic dermatitis) is unquestioned; but whether this parenteral infection causes the diarrhoea, results from the diarrhoea, or has no causal relationship, is not yet decided. It has been widely held, in this country at any rate, that it is causative; but authoritative opinion can be found for the other views as well.

Evans (1942) considers parenteral infection, especially respiratory, to be an important factor; he found it in every outbreak of non-specific diarrhoea he studied. Alexander and Eiser (1944) found parenteral infection (the bulk of it respiratory) in 124 out of 140 cases studied; they, too, think it an important factor. Gunn (1944a) found mastoiditis the most frequent post-mortem lesion, and thinks it important to treat this disease, even though he is not sure whether it is really causative. Smellie (1939) also was impressed by the frequent association of mastoiditis and severe gastro-enteritis, but finally gives this cautious judgment: 'The relationship between infantile diarrhoea and parenteral infection has not yet been elucidated. It is suggested that sometimes this infection is the cause, but sometimes it is the consequence.'

The view that the parenteral infection may be the result of the diarrhoea is supported by Fothergill (1944), who writes: 'In infants and children the most common complication of dysentery is an intercurrent infection. Infection of the upper respiratory passages and otitis media are fairly common.' Ouyang (1940), in his series of (mainly bacillary) enteritis, found bronchopneumonia the most common complication, and Frant and Abramson (1939) found pulmonary and otitic disease the most serious complication of epidemic diarrhoea of the newborn. Neter (1944) found the same complication in infants suffering from specific Salmonella infections: it is hard to see that parenteral infection could be responsible for that. It is possible that the frequent vomiting which is a feature of gastro-enteritis may cause bronchopneumonia and otitis by trickling into the trachea and upper respiratory passages; though Gunn (1946) points out that these complications are rare in non-infective, obstructive vomiting, as in pyloric stenosis.

The neutral view also does not lack support. In her review of over 200 cases, Gairdner (1945) found that 35 per cent. of her cases had parenteral infection, but that this made no difference to the outcome, and she is doubtful whether there is any causal relation. In 1933(b), Paterson wrote: 'The author frankly confesses that he does not understand why an infant with a nasopharyngitis or an otorrhoea, a mastoiditis or a furunculosis, or an infection in some part of the body remote from the intestine, should tend to have diarrhoea.' Mitman (1944) agrees: 'In my experience parenteral infections are found in about 30 per cent. only of cases, and proof is lacking that they are causal.' Some recent American investigators (Weihl et al., 1947) report that in their series diarrhoea was mild when associated with parenteral infection, and they consider that there is no causal relation between the two.

An analysis of the present series to show the effect of parenteral infection is shown in table 7. Parenteral infection is classified into three groups: Upper respiratory infection, of the larynx and above, including otitis and mastoiditis; lower respiratory infection, of the trachea and below, most being pneumonia; and skin infections, comprising impetigo, scabies, and infected eczema.

TABLE 7

ANALYSIS OF PARENTERAL INFECTIONS IN INFANTS SUFFERING FROM GASTRO-ENTERITIS

	Contracted in hospital		Contracted outside	
	Recovered	Died	Recovered	Died
With parenteral infection:	25	27	28	6
upper respiratory ..	5	6	16	3
lower respiratory ..	14	16	9	2
of the skin ..	6	5	3	1
Without parenteral infection: ..	6	19	32	13
'not doing well' ..	1	10	–	–
post-operative ..	–	1	–	1
others	5	8	32	12

The distinction between infants catching the disease in hospital, and those acquiring it outside, has been maintained, with the corrections made for relapses and for recent discharge, as mentioned previously. The table shows a number of interesting features:

1. The case mortality for gastro-enteritis with parenteral infection is 52 per cent. in hospital infection, 18 per cent. in outside cases; in either case it is lower than the case mortality without parenteral infection, when the rates are 76 per cent. and 29 per cent. (however, the figures for outside cases are not statistically significant). This agrees with the American opinion, quoted above, that enteritis with parenteral infection tends to be milder.

2. Of the seventy-seven hospital cases, fifty-two, that is 68 per cent., had a parenteral infection; while only thirty-four out of seventy-nine, that is 43 per cent., of the outside cases had this complication. This difference is significant. The trend of the figures might have been anticipated: as infants in hospital are, a priori, more likely to be already suffering from an infection.

3. The type of parenteral infection made no difference to the outcome: the case mortality is the same for all three types.

4. It is not possible to appreciate the true significance of parenteral infection in hospital-contracted disease without an idea of the composition of the hospital population. This is given in table 8.

Comparing the two tables, it appears that infants with skin or upper respiratory infections, and those without parenteral infection, caught gastro-enteritis in rough proportion to the risk they ran; but there was a strong association with pneumonia. Sufferers from this disease were particularly prone to contract gastro-enteritis. But it must be remembered that pneumonia and gastro-enteritis are both rife during the winter months; so the pneumonia patients were in the wards when the diarrhoeal infection was at its height, whereas the skin sufferers and those with upper respiratory infection were distributed much more uniformly throughout the year.

5. The commonest type of parenteral infection in outside-contracted disease was the upper respiratory. This is, indeed, the commonest infection in infancy, accounting for 24 per cent. of all

TABLE 8

RELATIVE COMPOSITION OF HOSPITAL POPULATION, BASED ON ADMISSIONS AND AVERAGE LENGTH OF STAY

	Total number of admissions in 24 months	Percentage of total	Average length of stay (days)*	Patient-days spent in hospital	Percentage of total
Upper respiratory infection ..	162	24	17	2,754	17
Lower respiratory infection ..	99	15	27·8	2,752	17
Septic skin conditions	89	13	38	3,382	21
Gastro-enteritis†	88	13	31·5	2,772	17
All others (general list)	236	35	18·9	4,460	28
Total	674	100		16,120	100

* The length of stay for gastro-enteritis patients is the average between stay of recovered cases, 46 days, and of fatal cases, 16·5 days.

† The importance given to gastro-enteritis in this table has been under-estimated, for no account has been taken of the large number of cases of this disease contracted in hospital.

infant admissions, and it was present in nineteen out of seventy-nine admissions for gastro-enteritis, that is in 24 per cent. It seems possible that a random sample of the population of the area would show that one in every four infants was suffering from a 'cold-in-the-head.' It is hard to see in this association any etiological factor, particularly as the mortality of gastro-enteritis with upper respiratory infection is three out of nineteen, or 16 per cent., while it is 29 per cent. in the absence of parenteral infection, a significant difference.

6. The high mortality of gastro-enteritis in the puny infant, admitted because it was not getting on well, is very striking. Only one survived out of eleven who contracted enteritis.

Many factors affect the reliability of these two tables, and too much stress should not be placed on inferences drawn from them. It happened frequently that an infant admitted with one infection (or with none) contracted another: the enteric infection is not unique in this respect ! It happened too, that an infant was quite cured of its primary infection, and was about to leave hospital, when it contracted diarrhoea; this is particularly relevant to the long convalescence after pneumonia. The primary infection can hardly be held responsible for the subsequent enteritis. Nevertheless, the following conclusions seem justified: (1) parenteral infection is common in hospital-contracted diarrhoea, but only in so far as the population at risk already suffers from such infection ; (2) the type of parenteral infection has no effect on the mortality; (3) and the enteritis is milder than in those without parenteral infections. Remembering that parenteral infection is present also in the population generally, though to a less extent than in hospital, the same conclusions seem to hold for enteritis contracted outside hospital.

In this series, at all events, there appears no causal relationship between enteritis and parenteral diarrhoea. This is not to say that diarrhoea is never caused by parenteral infection; but when it is so caused the enteritis is mild, and is nosologically different from the severe gastro-enteritis here discussed.

Chemotherapy

Additional evidence about the nature of the infecting agent is given by its response to chemotherapy. It is important to distinguish between the specific dysenteries, and non-specific enteritis : opinion is united in acclaiming the sulpha-drugs in the former group, but is at variance when discussing the latter. Anderson (1941) thought that sulphathiazole was of value, but his cases are few and the disease mild. Taylor (1941) agrees with him, as do Halpern and Cunningham (1942), but Cooper et al. (1941) found it useless in non-specific enteritis. It is interesting to see that no pathogen was found in five out of the six fatal cases in their series. Meyer (1943) reports very favourably on sulphathiazole and sulphaguanidine; however, he considers half his cases at least to be due to Shigella infections. Henderson (1943) found sulphaguanidine of great value in infantile diarrhoea of all types, so does Tudor (1942). On the other hand, Rubens et al. (1943) state that, while chemotherapy was very useful in dysentery cases, it was of no significant avail in non-specific cases. Menchaca (1944) used sulphadiazine on a few cases with good results, as did Tudor (1943) with sulphadiazine and sulphapyrazine. Twyman and Horton (1943) found sulphasuxidine of value in a small series; they do not discuss bacteriology. Marshall et al. (1941) used sulphaguanidine on sixteen dysentery patients with good results, and on three non-specific cases with indifferent results. Burns and Gunn (1944) obtained equivocal results with sulpha-drugs and penicillin in enteritis with severe otitic complications; Gunn (1944b) obtained no improvement with sulphaguanidine or sulphasuxidine, but recommends the use of a soluble sulpha-drug to combat any concomitant respiratory infection. Anderson and Nelson (1944) used sulphasuxidine in an outbreak of diarrhoea among seventy-six infants. They are reluctant to lay much stress on its value, for some patients needed long courses before they improved, and others actually contracted the disease while on full doses of the drug. High et al. (1946) found both sulpha-drugs and penicillin useless in neonatal diarrhoea. The value of both the soluble and insoluble sulpha-drugs in dysentery is admitted by all these investigators, as it has been in adult medicines. But it is plain that in severe non-specific enteritis their value is dubious. The impression left after reading these accounts is that in severe gastro-enteritis chemotherapy is of no avail. The present series was treated in the early days of sulphonamide treatment, and the relatively insoluble preparations were not in general use. Sulphapyridine was very frequently used for respiratory infections, and it was no uncommon occurrence for an infant to develop enteritis while taking this drug. This experience agrees with the findings in the literature, that the soluble sulphonamides are useless in non-bacterial enteritis.

Value of Blood and Blood Products

There is some evidence that blood and blood-products are of particular value in infantile enteritis. Felsen and Wolarsky (1941) used lyophile plasma and found it very effective; Lyon and Folsom (1941) found that citrated blood from patients recovering from influenza was very effective, while that from non-influenza sufferers was useless. This would indicate that specific immune bodies are concerned. Alexander and Eiser (1944) used plasma freely for shock, and considers its use an important factor in producing their low case mortality. On the other hand, High et al. (1946) found gamma-globulins to be useless. In the present series, transfusions were given to eleven desperately ill infants, and seven recovered. The numbers are small, and the cases are without controls, but there remains a strong clinical impression that without transfusion all would have died.

'Epidemic Diarrhoea of the Newborn'

Reference has frequently been made to 'epidemic diarrhoea of the newborn.' The first account to deal with this as an entity was by Rice et al. in 1937. A further account was given by Frant and Abramson in 1939, and an authoritative statement by them appeared in 1944. Other general descriptions have been given by Lyon and Folsom (1941) and by Felsen and Wolarsky (1942); this last paper includes an excellent bibliography. There is a striking unanimity in all these reports; they present a highly infectious disorder occurring during the first month of life, in maternity nurseries, and other institutions dealing with neonates. The mortality is usually about 45 per cent. and premature babies in particular suffer very heavily. There is no sex difference, no seasonal incidence, and breast feeding does not fully protect. All writers stress that this disease does not occur after the age of twenty-eight days. No protective measure, other than completely closing the institution, is of any avail in stopping the epidemic. These first reports all come from New York, but epidemics have been reported elsewhere: in Philadelphia (Anderson and Nelson, 1944; High et al., 1946); in Los Angeles (Johnson and Rothman, 1940) and in Milwaukee, Wisconsin (Cron et al., 1940). In this last epidemic, no breast-fed baby died.

Accounts of this malady are not confined to the U.S.A. McClure (1943) described four outbreaks in Ontario. In England epidemics have been reported by Craig (1936), Ormiston (1941), Crowley et al. (1941), Bloch (1941), and Sakula (1943). As previously mentioned, one outbreak occurred on the high seas. In this country, too, the findings agree closely, particularly in the failure to implicate a definite pathogen in spite of the obviously infective nature of the disorder. The suggestion has repeatedly been made that a virus is responsible.

At first glance, it does look as though this disease were indeed a true nosological entity, separate and distinct from gastro-enteritis as it appears in the older infant. But further comparison does not bear this out. Both diseases are highly infectious, and can be controlled only by closing the nursery and dispersing its inmates; in neither has a bacterial pathogen been found, and in both a virus is suspected. The clinical description of epidemic diarrhoea of the newborn fits very well the severe type of gastro-enteritis seen by Gairdner in West Middlesex, or that witnessed in North Kensington and described in these articles. There are two main differences; the first of these concerns the age incidence. Naturally, an outbreak occurring in a maternity hospital will involve babies under four weeks old—they are the only ones there. It is hard to see what sudden change occurs in a baby at twenty-eight days to make it immune to a disease to which it was previously so susceptible. The second factor concerns the protection normally afforded by breast feeding. It is plain that a baby only two weeks old cannot have been breast-fed for six weeks, and so cannot have the protection given by this period of nursing. Putting the comparison another way: if the severe type of hospital-contracted diarrhoea herein described had occurred in a nursery for neonates it would have been indistinguishable from 'epidemic diarrhoea of the newborn,' as already defined. It has already been stressed that infectious gastro-enteritis tends to occur in concentrations of susceptibles; and the highest concentrations of all are to be found in maternity nurseries. It is this fact which has given outbreaks of infectious diarrhoea in such nurseries their apparently unique features. It should be noted that neonates are rarely found in hospitals, other than in maternity nurseries. In the present series, there were only five infants aged one month, and only three younger than that. The hospital has no maternity department, and although from time to time young infants were admitted because their mothers were ill, as a rule they kept well. Such healthy nurslings were not kept in the general children's ward, but in the side-rooms of adults' wards, and probably owe their immunity from infectious diarrhoea to this precaution.

Conclusions

The following conclusions seem justified:

1. 'Diarrhoea and enteritis under two years' is a heterogeneous group.
2. Most of the severe cases of this group belong to an acute infectious (probably specific) disorder, which carries a case-mortality of 33-50 per cent.
3. This disease occurs in definite small epidemics, at different times in different places, but mainly in early winter.
4. Congregation of susceptibles favours the development of an epidemic; so the disease is found, with increasing frequency, in overcrowded cities, in children's hospital wards, and particularly in the nurseries of maternity hospitals.
5. The pathogen is non-bacterial, and may well be viral. The route of entry is not oral, but probably respiratory. The brunt of the infection falls on the intestine, its regional lymph glands, and the liver.
6. The value of chemotherapy is very doubtful, but blood transfusion seems to exert a specific effect.
7. There is no good evidence that this disease is caused by parenteral infection.
8. There is no good reason for considering 'epidemic diarrhoea of the newborn' to be a separate entity. This term merely describes what happens when severe gastro-enteritis breaks out in a maternity nursery.

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SALICYLATE THERAPY IN CHILDREN

BY

GIORGIO F. MAGGIONI, M.D., D.C.H.*

(From the Children's Hospital and Department of Paediatrics and Child Health, University of Birmingham)

For more than half a century salicylate compounds have been used empirically in the treatment of rheumatic fever. Although there is almost general agreement (Griffith, 1947) that they have analgesic and antipyretic properties, inducing symptomatic relief, especially in the presence of polyarthritis, yet the mechanism underlying their effect is still unsolved and there is no satisfactory explanation of their action on the rheumatic process. In the last few years the question has once again been raised following Coburn's statement (1943) that high doses of sodium salicylate (0·19 g. to 0·14 g. per kilo of body weight, sufficient to raise blood levels to 35 or 45 mg. per 100 ml. of plasma) would be able 'to modify the sterile inflammatory reaction which occurs during activity of rheumatism,' thus preventing the subsequent development of cardiac disease. His advice to use high doses of sodium salicylate is not original, since many authors in the past have emphasized the necessity of such massive or even larger doses to obtain the best results rapidly (Lees, 1903; Clarke, 1906; Peters, 1929; Wilkinson, 1935). Coburn achieved a correlation between salicylate therapy and concentration of the drug in the circulating blood, and considered that information about the salicylate plasma concentration was essential for a rational therapeutic scheme.

Coburn's opinion was partly supported by Taran and Jacobs (1945), Manchester (1946), and Peters (1947), while other authors emphasized the inefficiency and even the dangers of such massive therapy (Wégria and Smull, 1945; Murphy, 1945; Harris, 1947). In the meanwhile new and simpler methods of estimating the salicylate, both in blood and urine, have been developed, thus making it possible to review the clinical pharmacological work of Baldoni (1908 and 1914), Hanzlik (1926), and Quick (1932a, b, and c, and 1933). New and interesting observations have also been reported by Kapp and Coburn (1942), Smith et al. (1946), Lester et al. (1946), and other authors on the absorption, excretion, and the metabolism of the salicylate compounds, and on the blood levels, especially in adults.

Considering the frequency of the beginning of rheumatic disease in childhood (Cohn and Lingg 1943), a study of the salicylate levels in blood and urine during salicylate treatment is of particular interest in that age group. Some observations are presented in this paper on the fate of salicylate drugs in normal and rheumatic children, but without any attempt to discuss the efficacy and specificity of this therapy. No restrictions were placed on food or liquid intake during these observations.

Methods of Estimation

Salicylates in blood. A very extensive literature exists on the quantitative and qualitative estimation of salicylates (Beilstein, 1932; Allport, 1945). For the estimation in blood we have employed the method of Brodie et al. (1944), now used in routine practice, with some modifications as follows, using the Evelyn photo-electric colorimeter to measure the colour density of the solutions.

To 1 ml. of plasma, collected over heparin (potassium or sodium oxalate influences the colour reaction) or 1 ml. or less of serum, add 0·5 ml. of 6 N HCl and 30 ml. ethylene dichloride in a small separating funnel. The use of ethylene dichloride for extracting salicylates was first advised by Stoecklin in 1912. Shake vigorously for five minutes and allow to separate. Run the ethylene dichloride layer into another funnel through a small cotton-wool plug. Treat the ethylene dichloride solution twice with 10 ml. of water and 0·2 ml. of 1 per cent. ferric nitrate in 0·07 N HNO_3. Separate and run the coloured water layer into the colorimeter tube and compare with a standard curve prepared in the same way.

Total salicylates in urine. As pointed out by Brodie et al. (1944), free salicylate in non-hydrolysed urine cannot be determined by their method, but we have confirmed the statement of Lester et al. (1946) that it can be used for the estimation of total salicylate in hydrolysed urine if the pH is adjusted to 4·6. We have therefore used Lester's method for the estimation of total salicylate in urine, acidifying with hydrochloric (Galimard, 1944) instead of sulphuric acid. The details are as follows:

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* Assistant in the University of Rome Clinica Paediatrica (Director, Prof. G. Frontali), and holding a British Council Scholarship, 1946-1947.

To 5 ml. of urine add 1 ml. concentrated HCl and hydrolyse for one to one and a half hours under a reflux condenser. Cool, and make to 50 ml. with water. Extract 2 ml. twice with ether, transferring the ether solution to a colorimeter tube. Warm the ether slightly in a warm water bath and blow air through it to evaporate off the ether. Dissolve the residue in water (5 or 6 ml.), adjust the pH if necessary to 4·6, and add 0·2 ml. of the ferric nitrate reagent as for blood, etc.

All estimations in this paper are expressed in terms of salicylic acid.

Drugs. The intravenous administration of salicylate is not used in this hospital, having no practical advantage. The drugs used orally in the routine treatment of rheumatic fever in this hospital are: (a) sodium salicylate with sodium bicarbonate (1:2) in liquid mixture of which 0·5 oz. is said to contain 20 gr. (=1·3 g.) of the drug; (b) aspirin, 5 gr. (=0·325 g.) per tablet; (c) calcium aspirin, 5 gr. per tablet (=0·325 g.).

Specimens of these compounds were collected from different wards and from different nurses and estimated for their actual content of the drug. Four specimens of sodium salicylate mixture contained 15·0, 15·7, 15·7, and 14·7 gr. of sodium salicylate instead of 20 gr. The aspirin tablets gave an average of 6 gr. of aspirin per tablet instead of 5. A child of nine years, therefore, will receive daily 96-100 gr. instead of 120 gr. of sodium salicylate, and 72 gr. instead of 60 gr. of aspirin. We were also able to show that with time the sodium salicylate solutions deteriorate. A diminution of 13 per cent. in one month was observed. Moreover, traces of the drug were usually left in the medicine glass. On the whole the difference between the theoretical and actual therapy may amount to a loss of about 20 per cent. Therefore it is advisable to use sodium salicylate in tablet form or in freshly prepared solutions, and the importance of shaking the bottle at the time of administration and of not leaving residue in the medicine glass needs emphasis.

Absorption and Excretion

The intake by mouth of sodium salicylate in water is followed rapidly by its absorption, and its presence can be detected after fifteen or twenty-five minutes in blood and urine. The peak in the blood level is reached in from one and a half to two hours, and decreases slowly. It is not a new discovery that in children aspirin and calcium aspirin are absorbed at a slower rate, as shown in fig. 1, and that the peak in the blood remains at the same level longer, falling more slowly (Smith et al., 1946).

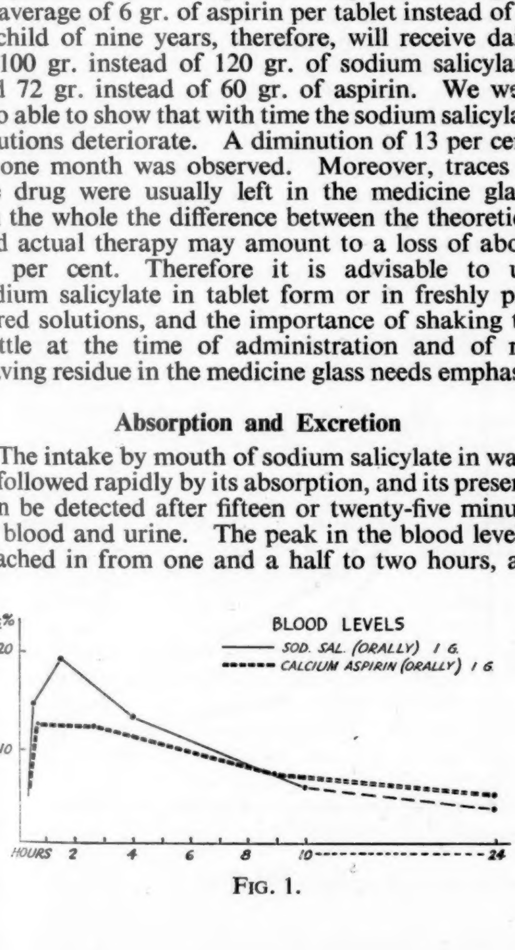

FIG. 1.

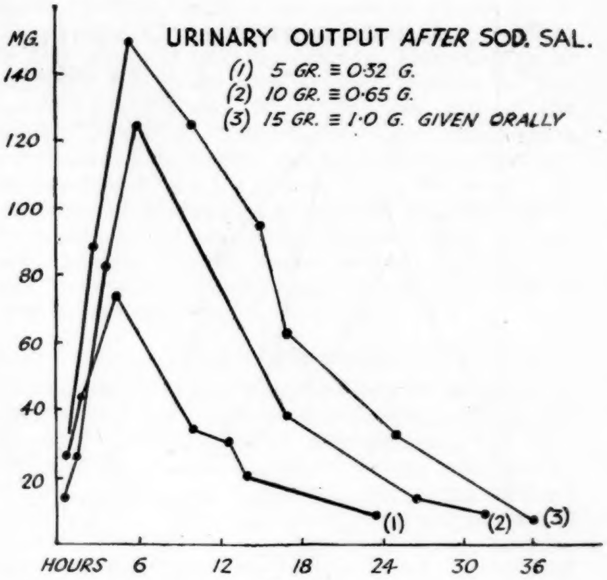

FIG. 2.

There is a relation between the doses of salicylate intake and the duration of excretion, the latter being proportionally longer with a larger dose. In a child convalescent from an acute disease other than rheumatic fever, we found that the time required for the complete excretion of a single dose of 1 g. of sodium salicylate was from thirty to thirty-six hours, whereas with 0·5 g. no salicylate was detected in the urine after twenty-four hours.

In figs. 2 and 3 are shown the hourly excretions after different doses of sodium salicylate or aspirin in the same subject. These data are in accord with the findings of Lester et al. (1946) for adults after taking aspirin. After oral sodium salicylate, practically no differences were observed between the free salicylate of plasma and total salicylate after hydrolysis of plasma. The possibility that some acetyl salicylic acid is absorbed without alteration or is present in conjugated form is supported by the observation that either after a single dose or after continuous treatment differences were discovered between total "salicyl" and free "salicyl" amounting to 10 or 15 per cent., which is considerably more than estimation errors. The possibility of acetyl salicylic acid disappearing from the plasma in a short time after absorption, as suggested by Lester et al. (1946), seems to be remote if treatment with the drug is continuous, although incubation in vitro of plasma with aspirin shows that hydrolysis does take place in a short time. Our results are not in accordance with those of Smith et al. (1946).

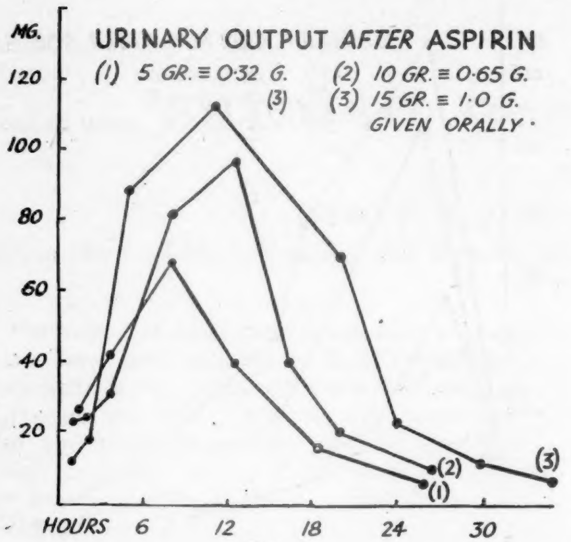

FIG. 3.

The increase of blood level with general routine therapy, that is, intake every four hours of sodium salicylate or of calcium aspirin, is shown in fig. 4. This appears to be steady during the first two or three days, and then the daily individual variation ranges between 10 and 15 mg. per 100 ml., even many weeks after the start of the treatment. These variations are mostly related, in our experience, to the time of the ingestion of the drug. This correlation is not mentioned by other authors.

These results are in agreement with those of Coburn (1943), Butt et al. (1945), and Lester et al. (1946), and in contrast with those of Stevens and Kaplan (1946) and of Erganian (1947).

In fig. 5 are shown the plasma levels of several patients treated with large doses of sodium salicylate or calcium aspirin for periods up to two months or more. The danger of any cumulative effect and the occurrence of toxic symptoms is small. On administration being stopped after many weeks' treatment, the drug completely disappeared from the blood and urine in from forty-eight to seventy-two hours (see figs. 6 and 7).

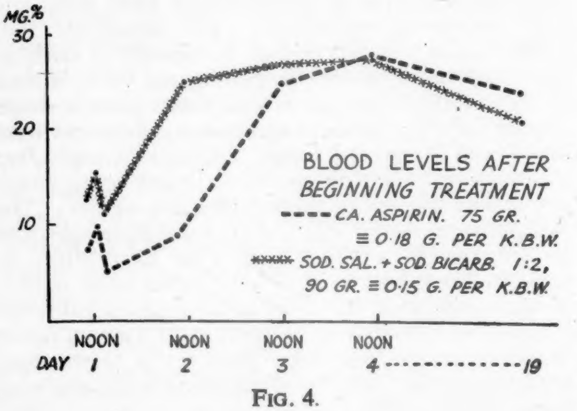

FIG. 4.

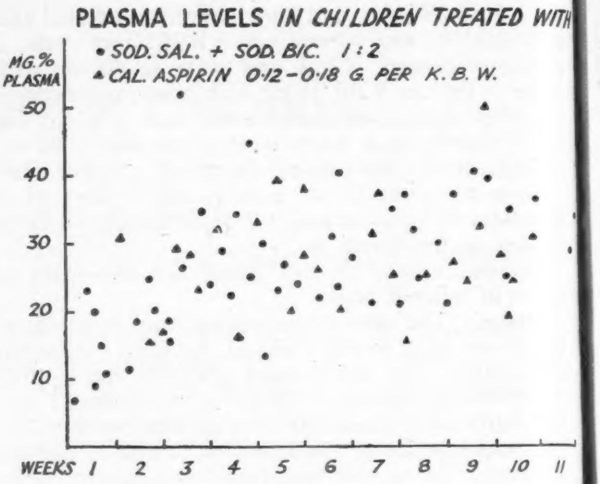

FIG. 5.

The quantity of salicylate that can be recovered from the urine of normal subjects taking single doses is about two-thirds of that ingested. Variation in percentage of the excretion showed no correlation to dosage or to urinary volume; but forcing fluid intake seems to produce a quicker excretion.

In rheumatic patients treated continuously, the salicylate recovered in the urine amounts to 50 or 60 per cent. or less of the intake, especially during acute periods. These observations are in accordance with those of Hanzlik (1926), and Coburn (1943), in adults. The low level of excretion seems to be due, in Coburn's opinion, to a more extensive modification of salicylate rather than to storage, as the time of disappearance after stopping the

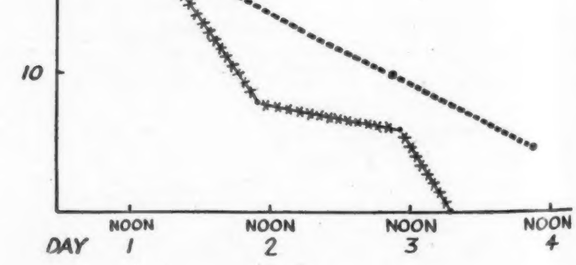

FIG. 6.

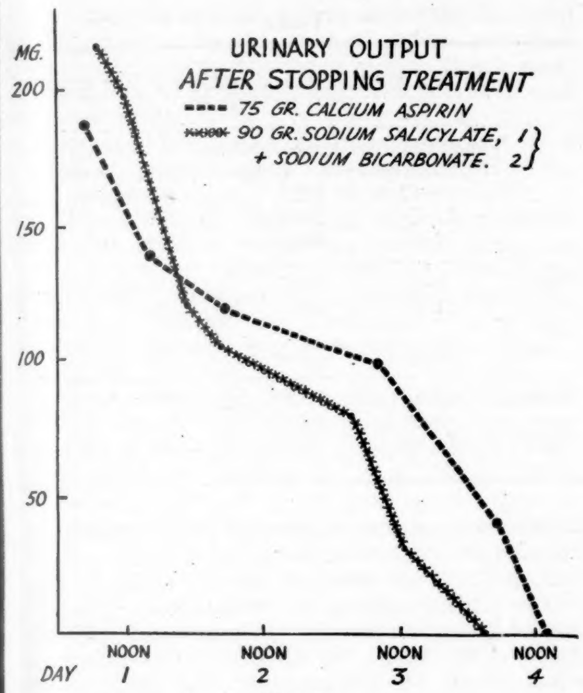

FIG. 7.

medication is not increased. It has been suggested that the rheumatic disease contributes to this increased destruction of salicylate, but it was observed that other patients, with fever not reduced by this drug, also showed a low salicylate output, Kapp and Coburn (1942).

The relation between intake of salicylate and body weight in our cases produce plasma values slightly lower in children than in the adults, even considering individual variations amounting to more than 10 mg. per 100 ml.

To obtain a steady blood level of at least 25 mg. per 100 ml., it is necessary to give a daily dosage of 0·12 to 0·18 g. per kilo of body weight (1 to 1·5 gr. per pound of body weight), which is approximately the dose that has been used for a long time in this hospital.

With due regard to individual differences in absorption and excretion, an insufficient salicylate level in the blood corresponds to an inadequate intake or inaccurate administration.

Concerning absorption of sodium salicylate administered per rectum, there is no accord of opinion (Mackenzie, 1943; Huntington et al., 1946). The argument was recently reviewed by Mackenzie, who obtained in children, with other methods, high individual variation in absorption. In our cases salicylate could be detected in the urine thirty minutes after rectal administration of a 1 per cent. solution without sodium bicarbonate in tepid water, the quantity increasing considerably between six and eight hours (fig. 8).

It is possible to obtain with continuous treatment (four enemata daily) a serum level up to 15 or 20 mg. per 100 ml. after administering 0·16 to 0·20 g. per kilo of body weight. The quantity of salicylate recovered after a single dose in normal subjects was between 50 and 60 per cent. of the intake, which is only slightly less than when administered by mouth, and it takes approximately twenty-four hours for a dose of 1 g. to disappear. The rate of absorption of sodium salicylate given by enema is not materially different from the rate when given by mouth, so this method of administration may have a place in the treatment of patients with severe vomiting.

Effect of Bicarbonate

Smull et al. reported in 1944 that the administration of sodium bicarbonate with sodium salicylate to both rheumatic and non-rheumatic subjects resulted in a lower concentration of salicylate in plasma than when salicylate was given without bicarbonate. They did not estimate the output of salicylate in the urine. From a more detailed review of the literature we find that in 1875 Fleischer reported a shortening of the period of excretion from thirty-six to fourteen hours when the patient was given bicarbonate. Also Ehrmann in 1907, and Morris and Graham in 1931 made the same observations. Recently other authors (Smith et al., 1946; Lester et al., 1946, etc.) have confirmed there is an increase of salicylate excretion in the urine of rheumatic patients who were given bicarbonate; and Lester et al. (1946) showed that in normal subjects taking acetyl salicylic acid with sodium bicarbonate (1:2), there is an increase of more than 50 per cent. in the rate of elimination.

In our cases the intake of a double proportion of sodium bicarbonate seemed to increase the rapidity of the absorption, and the blood salicylate reached the same level as it did without sodium bicarbonate, but these blood levels decreased with greater rapidity (fig. 9), diminishing even to half the other levels after from four to six hours. We have also found an increased rate of excretion in the urine in the first twelve hours. (These excretions are in

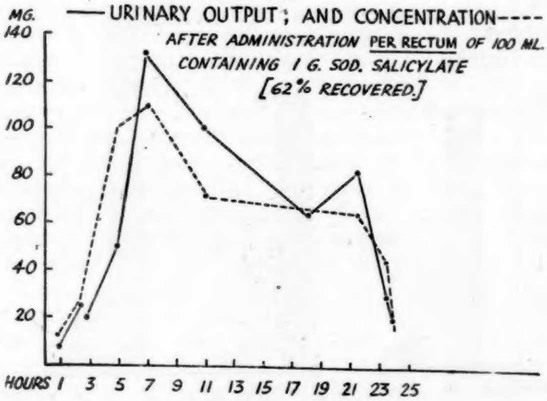

FIG 8.

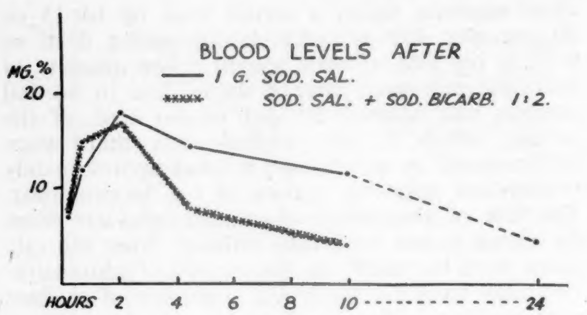

FIG. 9.

excess of any individual variations found in any of the subjects studied.)

From fig. 10 there appears to be a certain relation between the proportion of the added sodium bicarbonate and the rapidity of the excretion, which is considerably slower when the salicylate and bicarbonate are present in equal quantities (1:1) and almost nil with half doses. From our experiments, giving single doses of sodium salicylate together with different quantities of sodium bicarbonate, we observed that the salicylate recovered from the urine was increased relatively to the increase of the sodium bicarbonate. It is difficult to say whether that was due to a better absorption from the intestinal tract or to an impaired destruction after giving sodium bicarbonate, particularly in view of the increased rapidity of evacuation from the stomach (Lolli and Smith, 1946) following the intake of alkaline substances. Using magnesium oxide as anti-acid in double proportion, the rate of excretion and the quantity recovered were the same as with a small quantity of sodium bicarbonate (fig. 11).

The more rapid excretion of the salicylate in the first twelve hours after giving a double dose of sodium bicarbonate (fig. 7) is often accompanied by a larger output of urine (see table). We must conclude, therefore, that in children the sodium bicarbonate not only relieves the gastric disturbance but also exerts some influence on the rate of excretion, and to a less extent on the absorption. These two results are apparently contradictory in view of the aim to attain maximum efficiency with minimum doses of the drug. We consider that a mixture of equal parts of sodium salicylate and sodium bicarbonate (1:1) given every four hours is sufficient to relieve the gastric trouble without exerting any appreciable influence on the excretion; the proportion may be 1:2 if the interval is reduced to two hours.

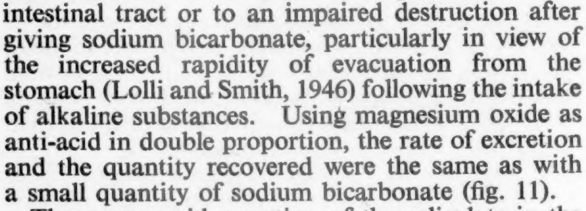

FIG 10.

TABLE

	Subject given 2 g. sod. sal. (=1·729 salicylic acid) by mouth		
	Time intervals (hours)	Urine volumes (ml.)	Salicylate recovered
Alone	0–12	867 } =1,197	489 mg. } =61%
	12–24	330	289
	24–42	950	264
With 4 g. sod. bic.	0–12	990 } =1,430	811 mg. } =71%
	12–24	440	333
	24–45	1,040	77
With 4 g. MgO	0–12	600 } =950	525 mg. } =58%
	12–24	350	361
	24·48	890	136

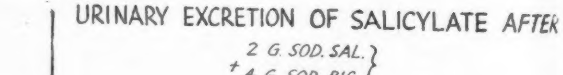

FIG. 11.

If we consider as a detoxifying action the increased rate of excretion by the urine of sodium salicylate given with double proportion of sodium bicarbonate, we should be in agreement with Peters (1947), who attributes a detoxifying property to the sodium bicarbonate. But we are of the opinion that there is rather an indirect action increasing the pH of the urine, and hence the excretion, especially considering that, following the concurrent administration of ammonium chloride, there is a reduction of the rate of output and an increase of the salicylate in the blood (Smith et al., 1946). Gubner and Szucs (1945) have reached the conclusion that sodium bicarbonate is ineffective in decreasing the toxicity of salicylate.

From the hypothesis that sodium bicarbonate in great amount increases the extracellular fluid, thus producing a decrease of the salicylate level in the circulating blood (Smull et al., 1944; Peters, 1947), and the demonstration of a quicker output through the kidney, as shown by our observations and those of other authors, producing a rapid increase of the renal clearance with increase of the pH of the urine, we believe that the effect of the sodium bicarbonate is more concerned with the mechanism of the secretion than with the disturbance of the water balance of the body.

Finally, the action of some other drugs (papaverine, spartein, glucose, etc.) on the fixation of sodium salicylate by the heart has been shown by the experimental work of Mercier et al. (1941). The possible influence also of bicarbonate needs further study.

Salicylate Intoxication

Many disturbances following salicylate therapy have been described since the introduction of these drugs to medicine, related either to high variation of individual susceptibility or to excessive doses. Tinnitus, nausea, anorexia, headache, vomiting, hyperventilation, nervous disorder, oedema, albuminuria, the presence of reducing substances in the urine, etc., are the most frequently described symptoms. In paediatric practice, anorexia, nausea, and vomiting are the commonest disorders, the latter sometimes of such a degree as to interfere with the administration of the drug by mouth. There is a difference of opinion, even after the most recent gastroscopic studies (Douthwaite and Lintott, 1938; Paul, 1943; Caravati and Cosgrove, 1946) as to whether salicylates affect the gastric mucosa, but the fact of gastric upheaval is established without doubt by clinical observation. It is also known that vomiting appears with the same, or even greater frequency after intravenous administration (Taran and Jacobs, 1945; Caravati and Cosgrove, 1946) without any salicylate being present in the gastric contents. Thus, it is fairly generally accepted that vomiting is more related to the action on the cerebral centres than to a local effect on the alimentary tract. From our observations it would seem that there is no constant relationship in the same subject between the height of the salicylate blood level and the beginning of vomiting, but that the severity of the toxic symptoms in the same subject is greater when the plasma salicylate level is high. In our experience, the vomiting appears more often at the beginning of treatment, and later disappears even with higher levels of salicyl in the blood, even in patients taking double proportion of sodium bicarbonate from the beginning of treatment.

The whole question of salicylate intoxication was recently reviewed by Rapoport et al. (1943) and Guest et al. (1945) who have brought new experimental support to the idea of a respiratory alkalosis developed by hyperpnoea with a lowering of the carbon dioxide tension, which may or may not be accompanied by a decrease of bicarbonate. In our patients who developed toxic symptoms, alkalinity of the urine was a common finding.

A few words must be added about other relatively recent information on the effect of salicylate therapy.

Prothrombinopenic action of the salicylate drugs. Since the first experimental observation of Link (1943) many authors have confirmed that in patients treated with salicylate drugs there is a decrease of prothrombin in plasma (Shapiro et al., 1943; Meyer and Howard, 1943; Jager and Alway, 1946; and others). Severe cases of haemorrhagic damage during salicylate treatment and considered to be due to prothrombin deficiency have been reported only rarely, while haemorrhagic manifestations have been observed in many instances. These were sometimes considered as caused by the disease, rather than by the therapy or by other mechanism (thrombocytopenia). The correctness of attributing the haemorrhagic manifestations to prothrombin deficiency is debatable (Shapiro et al., 1943; Coombs et al., 1945; Butt et al., 1946; Peters, 1947; and others). The mechanism of the action of the salicylate on the prothrombin is not clear. Shapiro et al., (1943) stated that patients with hepatic damage, and according to Link et al., (1943) animals with vitamin K deficiency, are more sensitive to salicylate prothrombinopenic action. The rapid elevation of prothrombin after stopping salicylate therapy is rather against an effect through hepatic damage (Clausen and Jager, 1946). Advice to administer vitamin K during salicylate therapy as given by Shapiro 1944 and Zimmerman and Shapiro (1946), is not generally accepted (Higley, 1945).

In the experience of physicians of this hospital (Wilkinson and Smellie) and those of the Clinica Pediatrica, Rome (Frontali), there is very little danger of haemorrhagic manifestation.

Ascorbic acid and salicylate drugs. Since the first communication of Daniels and Everson (1936) on the influence of aspirin on the urinary excretion of ascorbic acid, other authors have confirmed that salicylate drugs increase the urine output of, vitamin C (Keith and Hickmans in this laboratory 1938; Samuels et al., 1940; and Noferi, 1944-45). We can confirm that in patients treated by salicylate there is also a decrease of the vitamin C in the blood even after adding vitamin C to the diet (25 to 50 mg.) (unpublished data), thus pointing to the advisability of administering vitamin C to these subjects in larger quantity. According to Gubner and Szucs (1945) ascorbic acid has a detoxifying action on salicylates.

Thiamine and salicylate drugs. Another question still requiring study is the relation between the salicylates and thiamine. Cleland (1943, 1946), in clinical and experimental researches, observed that over short periods of time salicylates increased the excretion of thiamine in urine but over long periods of therapy they caused a reduced output, presumably due, according to her, to a loss of body stores during the preliminary period of increased excretion.

Lutwak-Mann (1942) injected rats with acetyl salicylate and found that after four and seven hours blood pyruvate values were lower than the control, but after twenty-four hours these were equal to the control.

We have had the opportunity of estimating the pyruvic acid in the blood (unpublished data) of subjects taking salicylate for long periods and have found values within the normal range.

Enzymes. The proof that other changes in metabolism are produced by salicylate was provided by the results obtained of numerous experiments by Lutwak-Mann (1942), and Euler and Ahlstroem (1943), of the influence of salicylate on enzymes. Recently Guerra (1946), and Dorfman et al. (1947) have proved that sodium salicylate inhibits in vivo the diffusive effect of hyaluronidase, this proof opening up a new possibility for the interpretation of the mechanism of the action of salicylate in rheumatic fever.

The disappearance within four to seven hours after the injection of salicylate in rats of nearly all the liver glycogen, and its full restoration within twenty-four hours, indicates an effect on several as yet unidentified enzymic processes. We can confirm the above results of Lutwak-Mann after giving a massive dose of salicylate by lavage to rats (Hickmans, 1947, unpublished data).

Conclusion

An appropriate scheme of salicylate therapy in children with rheumatic fever should include:

1. The oral use of freshly prepared solutions of sodium salicylate in flavoured water with sodium bicarbonate added in the proportion 1:1 when given every four hours, or 1:2 when given every two hours. The last dose in the evening and the first in the morning may be double to permit a longer interval during the night. The administration by enema seems to be indicated in patients with severe vomiting. Aspirin or calcium aspirin in tablets can also be used.
2. The quantity of sodium salicylate which in children raises the level up to 25 or 35 mg. per 100 ml. is in the range of 0·12, 0·18 gr. per kilo of body weight. The estimation of salicylate plasma level seems advisable, to control the accuracy of the administration and to avoid over-dosage.
3. The patients should have plenty of fluid, with addition of sugar or fruit juice.
4. There should be a supplementary administration of vitamin C in order to avoid the depletion of ascorbic acid reserves.

In the experience of some authors, the giving of vitamin A in addition seems to be useful. The administration of vitamin K to prevent prothrombin diminution is necessary only after control of the prothrombin time.

5. In case of any sign of intoxication—the frequency of the respiratory movement should be observed—the administration of high doses of sodium bicarbonate together with fluid, given if necessary parenterally, can accelerate the excretion of the salicylate from the body.

Summary

The absorption and excretion of sodium salicylate and aspirin, given orally and per rectum, to rheumatic and non-rheumatic children, either in single doses or continuously, was investigated.

To attain a level of 25 to 35 mg. per 100 ml. of plasma, it is necessary to give 0·12 to 0·18 g. per kilo of body weight (that is 1 to 1·5 gr. per pound body weight). When bicarbonate (1:2) is added, the blood level decreases more quickly than without bicarbonate, owing to the increased rate of excretion in the urine, especially in the first twelve hours.

The advisability of adding vitamins B, C, and K is discussed.

The author wishes to thank the Honorary Staff of the Children's Hospital for allowing him to use their cases and Professor J. M. Smellie for his helpful advice. He is also much indebted to Dr. E. M. Hickmans, Biochemist to the Children's Hospital, for her criticism and help throughout the work.

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THE pH OF THE MOUTH IN THE NEWBORN INFANT

BY

JOHN THOMSON, M.D., D.P.H., D.C.H.
(From the Department of Child Life and Health, University of Edinburgh)

Introduction

In an article on vaginal thrush, Liston and Cruickshank (1940) state that ‘ the organism finds an acid moist surface on which to grow in two situations—the mouths of suckling infants or invalids and the vaginae of adult women in certain circumstances.’ Further, they ‘ attach great importance to the pH reaction as a factor influencing the possibility of infection with Oidium albicans.’ Confining their attention to the question of vaginal thrush, they offer no evidence in support of the statement that the mouth of the suckling infant provides an acid moist surface, and no pH observations are given.

Published information with regard to the pH of the mouth of the newborn appears singularly scarce, the only reference the writer has found being that of Allaria (1907). Here it is stated that ‘ the reaction of the mouth in the newborn infant is neutral or slightly acid to litmus and in the nursling continues to react acid to litmus but does not turn methyl-orange. The pH is very slightly on the acid or the alkaline side, or indeed exactly at the neutral point (7·0), provided freshly secreted saliva is taken. After it remains in the mouth for a while it becomes distinctly acid.’

In view of the importance which Liston and Cruickshank attach to this aspect of the soil upon which the Oidium albicans flourishes so commonly, and because of the lack of readily available data, it seems desirable that some observations should be recorded.

Technique

The well known B.D.H. capillator method was used. Specimens of the oral fluid were taken from infants during the first nine days of life. These specimens were obtained by capillary tube and were taken never sooner than two and a half hours from the time of the last feed. They were all from infants who were being started on a three-hourly feeding regime. No observations on ill infants were included, neither were there any observations included where the infant was known to have vomited or regurgitated since the previous feed.

Results

The observations are portrayed graphically (fig. 1) to show the ‘ scatter ’ of the observations made as well as the daily average pH. It will be seen that in most instances (about two out of every three) the pH is initially in the neighbourhood of 6·8 and only rarely may be as low as 5·2. It will also be observed that it is more likely for the pH to be above the average figure of pH 6·5 for the first day, than below it.

By the second day the chance is equal, but after that it is more likely that the pH will be less than the average figure shown (see table).

The daily average figure shows a daily increase in acidity during the whole of the first week. By the end of this time a fairly constant range of pH has been reached, the level fluctuating from approximately pH 5·2 to pH 5·6.

In most instances curves obtained from individual infants follow the average trend (fig. 2). Now and

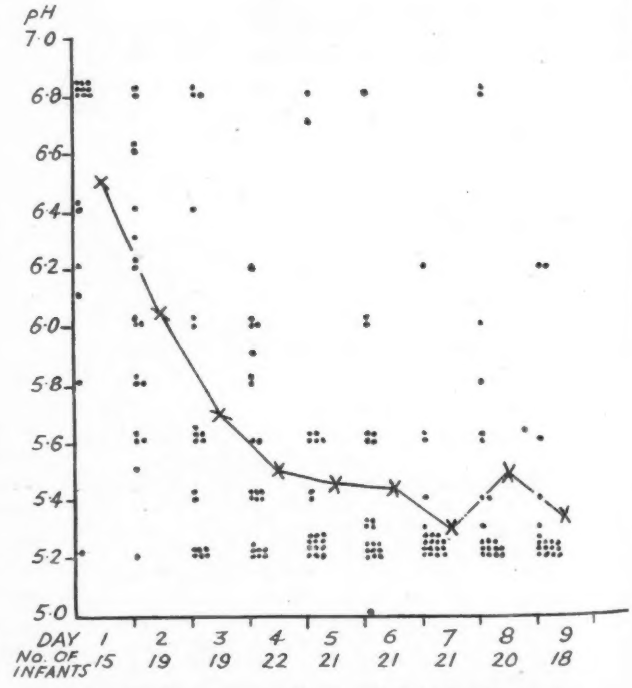

FIG 1.—Daily average pH of oral fluid in the newborn.

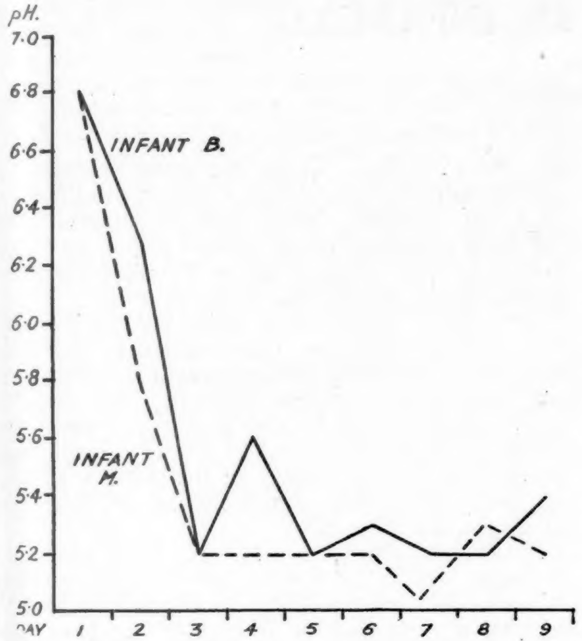

FIG. 2.—Daily variation of the pH of the month in individual infants.

TABLE
DAILY AVERAGE pH OF ORAL FLUID IN NEWBORN INFANTS

Day	1	2	3	4	5	6	7	8	9
Av. pH	6·5	6·04	5·7	5·5	5·45	5·44	5·3	5·49	5·35

then, however, somewhat erratic readings are obtained. For these no explanation is offered.

Summary

Some observations on the pH of the oral fluid in the newborn infant are recorded.

They show that the pH increases in acidity from day to day for the first seven days of life.

The statement of Liston and Cruickshank that the mouth of the suckling infant is a moist acid surface is substantiated in so far as the first nine days of life are concerned.

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AZOTAEMIA IN INFANCY*

BY

S. A. DOXIADIS, M.D.

(From the Department of Child Health, King's College, University of Durham)

It has long been known that infants with diarrhoea and vomiting show high levels of urea in their blood. Earlier investigators regarded this as due to dehydration (Schloss et al., 1918; Bessau et al., 1922) or to an attempt to retain at normal levels the blood osmotic pressure which was reduced as a result of salt loss (Hartmann and Smyth, 1926) while Wilmanns (1921) considered that the high blood urea arose from increased tissue protein breakdown due to passage of toxic products from the intestine into the circulation. The evidence presented in support of these theories was not satisfactory, and the conclusions were more or less a matter of surmise. More recently the approach to this problem has become clearer from studies on renal function in infancy (Young and McCance, 1942; Harrison et al., 1942) and from a closer understanding of extrarenal azotaemia in gastroduodenal haemorrhage. The latter work has been well summarized by Black (1942).

The present paper is an attempt to define the conditions under which azotaemia may develop in infancy and to explain its pathogenesis.

Material

The material for this study consists of all the sick infants under one year of age who on admission to the wards of this Department presented blood urea levels between 50 and 500 mg. per 100 ml. Forty-seven such cases were collected in a period of sixteen months. Another twenty sick infants, in whom the blood urea level was below 50 mg., have been studied as a control group.

Age Incidence

The age incidence is shown in fig. 1. The majority of cases occur during the first three months of life, when, moreover, the proportion of values over 150 mg. is much higher. The cause of this age incidence will be discussed later.

Factors Responsible for Azotaemia

As azotaemia is a symptom and not a clinical entity, an attempt was made to find a common link connecting all the forty-seven cases. A study was therefore made of the factors which might be responsible for the azotaemia.

URINE FINDINGS. Examination of a specimen of urine, collected as soon after admission as possible, yielded in most patients negative results. Slight albuminuria and a few pus and red cells, and/or occasional casts were noticed in some specimens, but these findings, which are quite common in infants suffering from a variety of infective illnesses, were not constant. They were encountered with the same frequency in the control group, and they did not indicate a kidney lesion of sufficient severity to account for the increase in blood urea.

ETIOLOGY. The primary illness was: in twenty-nine infants, infective gastro-enteritis; in four pneumonia; in three, meningococcal meningitis; in one, septicaemia; in one, congenital heart disease; in two, pyloric stenosis; and in seven, an unknown infection (in five acute and in two of a more prolonged type). The etiology of the primary illness, varying so much, does not, therefore, offer the link connecting all these cases.

DIARRHOEA AND VOMITING. As extrarenal azotaemia in infancy has hitherto always been reported in connexion with primary or secondary gastro-enteritis, the presence or absence of diarrhoea and vomiting was studied. These symptoms were a prominent feature of thirty-nine cases, twenty-nine of primary gastro-enteritis, and ten in which diarrhoea and vomiting was due to parenteral infection. In the remaining eight cases (three of pneumonia, three of acute unknown infection, one of meningitis, and one of congenital heart disease) the azotaemia developed in the absence of any

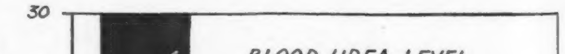

FIG. 1.—Age incidence.

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* This work was done during the tenure of a Luccock Research Fellowship, Medical School, King's College, Durham University. Part of the paper was communicated to the Annual Meeting of the British Paediatric Association at Windermere on April 25, 1947.

gastro-intestinal symptoms. The azotaemia is not, therefore, necessarily connected with primary or secondary gastro-enteritis.

Clinical picture. It was to be expected that the clinical picture of a group of cases of such varying etiology could not be the same. In spite of this a common factor, dehydration, was invariably present, under which general term are also included signs of circulatory embarrassment (collapse) due to dehydration of the intravascular compartment. The recognition of the importance of dehydration made a more accurate investigation necessary to see how far the degree of it was correlated with the degree of azotaemia.

Measurement of dehydration. No objective method for the measurement of dehydration is absolutely reliable, but a fair idea of the amount of plasma loss may be gained by the careful interpretation of haematocrit values, and of the total loss of body water from changes in the infant's weight. Assuming that the total red-cell volume is constant during changes in hydration it can be shown that the amount of plasma loss in dehydration expressed as a percentage of the normal plasma volume equals

$$100 - \frac{100\,h\,(100 - h')}{h'\,(100 - h)} \quad \text{where}$$

h = haematocrit reading in normal hydration.

h′ = ,, ,, in the dehydrated stage.

For h′ the haematocrit reading immediately after admission was taken, and for h the value after the infant seemed rehydrated clinically and the reading was practically the same in two successive days.

Total body water loss was calculated from changes in weight. In some subjects the normal weight before the onset of the illness was available, but where this was not so the weight gained following rehydration was taken to represent the total body water loss.

The blood urea values are plotted in fig. 2 against plasma loss expressed as a percentage of the normal (sufficient data for calculation in forty-four cases), and in fig. 3 against total body water loss expressed in per cent. of body weight (sufficient data for calculation in thirty-seven cases).

It can be seen in fig. 2 that, except in two patients, with rising blood urea the minimum plasma loss also increased, so that all infants presenting a certain blood urea level had a plasma loss over a corresponding minimum. For example, in infants in whom the blood urea level had risen over 50 mg. there was a plasma loss of at least 10 per cent., while when the blood urea was over 150 mg. there was a plasma loss of at least 30 per cent. (The dotted line has been drawn to make this correlation more evident.)

In fig. 3 the same correlation exists between azotaemia and total water loss, and here the two striking exceptions in fig. 2 (high blood urea without plasma loss) fall well into the general rule. Both patients were chronically dehydrated infants in whom the plasma volume had returned to normal at the expense of the extravascular compartment, which was depleted by 13 and 14 per cent. respectively of body weight.

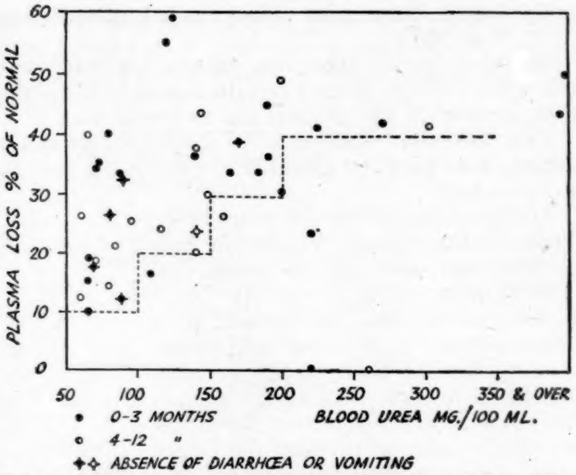

Fig. 2.—Blood urea volumes plotted against plasma loss.

From a closer study of figs. 2 and 3 two further points emerge.

(a) The distribution of the values for infants under and over three months is the same; younger infants, therefore, given the same degree of dehydration, do not tend to develop higher blood-urea values and the higher incidence of azotaemia during the first three months of life is due to the well established fact that younger infants become more easily dehydrated.

(b) The distribution of the values for infants with and without diarrhoea and vomiting was the same.

While azotaemia has always developed in this series in connexion with a corresponding minimum water loss, the reverse, as can be seen in figs. 2 and 3, did not hold, and a certain water loss did not necessarily cause a corresponding degree of azotaemia. For example, in marked dehydration with a plasma loss of from 30 to 40 per cent. or a total water loss of from 8 to 10 per cent. of the

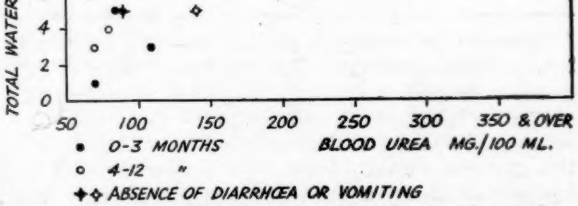

Fig. 3.—Blood urea volumes plotted against total water loss.

body weight, blood-urea values ranged as widely as from 70 to 300 mg.

An investigation, therefore, became necessary into the factors which, given a certain degree of dehydration, determine the ultimate rise in blood urea.

CONTRIBUTING FACTORS. As complete metabolic experiments were not possible, the following factors were studied.

1. Duration of the symptoms before admission. There was no direct correlation between duration of symptoms and height of blood urea.

2. Concentrating capacity of the kidney. Estimation of the urea content of a specimen of urine passed soon after admission gave values ranging from 1·08 to 4·65 per cent. The higher values were not necessarily obtained from the infants with the high values for blood urea, so that no relation existed between the height of the blood urea and the urea content of the urine. The response of the kidneys of sick infants to the stimulus of a high blood urea varies widely, therefore, in different individuals. This varying response is undoubtedly one of the factors determining the ultimate rise in blood urea in each case of dehydration.

3. Protein intake. It was impossible to assess the protein intake during the days preceding admission. The influence of protein intake on the blood urea was therefore studied after admission, during the period of rehydration.

Dehydration being the main cause of the azotaemia, it is natural to expect a fall in blood urea during rehydration; this was seen in twenty-eight cases out of the forty for which sufficient data were available, but in the remaining twelve cases there was a temporary but significant rise in the blood urea ranging from 20 to 70 mg. The protein intake of these two groups of cases, subdivided according to their age, is shown in table 1.

TABLE 1

EFFECT OF PROTEIN INTAKE (GRAMMES PER 100 ML. OF TOTAL FLUID INTAKE) UPON BLOOD UREA DURING REHYDRATION

Age group	Fall in blood urea (28 cases)	Rise in blood urea (12 cases)
0-3 months (25 cases)	17 cases protein intake less than 3·8%	8 cases protein intake 3·8–7·6%
4-12 months (15 cases)	11 cases protein intake less than 5·5%	4 cases protein intake 7–7·6%

It is evident from this table that all cases with rising blood urea were taking more than 3·8 g. of protein per 100 ml. of fluid intake if under three months of age, and more than 7 g. if older. It seems, therefore, that there exists a critical level in the protein intake, lower for young infants and higher for older, over which any excess may cause a rise in the blood urea. This critical level was more constant when expressed, as in table 1, as a fraction of total fluid intake, than in relation to the unit of body weight.

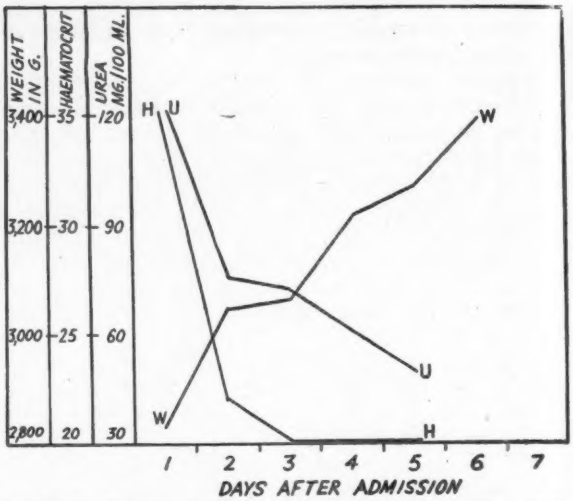

FIG. 4.—Changes in blood urea during rehydration (fall).

The influence of high protein intake on the blood urea under normal conditions of hydration was studied in two infants of eleven and five months old respectively, the first with mental deficiency and the second with congenital hydrocephalus. They were kept for five days on a constant caloric and fluid intake while the daily protein intake varied from 1·5 to 7·6 and from 3 to 7·6 g. per 100 ml. of fluid intake. The results are presented in table 2, where it is shown that even under normal conditions of hydration high protein intake causes a rise in blood urea up to double the normal value. In assessing the value of these results it may be recalled that protein milk preparations may contain as much as 7·6 per cent. of protein.

The data of tables 1 and 2 were obtained during rehydration and under normal conditions of hydration.

There can be no doubt that during progressing dehydration an even lower protein intake may have the same effect on the urea level of the blood.

In very few cases was there reliable information about feeding during the days before admission. The impression from these cases is that infants put on a water diet presented lower urea values than similar patients kept on milk feeds.

Course

It has already been pointed out that the blood urea falls following satisfactory rehydration when the protein intake does not exceed a certain level. In fig. 4 a typical case is presented; it can be seen that the depleted plasma, as shown by the haematocrit, quickly returns to its normal volume, but that the blood urea requires a longer time to return to normal and that its fall roughly parallels the rise in weight. It seems, therefore, that during rehydration the replenishment of the

TABLE 2

EFFECTS OF HIGH PROTEIN INTAKE ON BLOOD UREA UNDER NORMAL CONDITIONS OF HYDRATION

Subject's age (months)	Day of experiment	Weight (g.)	Haematocrit	Protein intake*	Blood urea mg. / 100 ml.	Urine urea g. / 100 ml.
R. K. (11)	1	7,450	30	1·5	30	1·38
	2	7,440	28·5	7·6	60	3·07
	3	7,450	29	7·6	74	3·20
	4	7,480	29·5	7·6	76	
	5	7,540	28	1·5	40	
J. L. (5)	1	6,250	32	3	26	
	2	6,250	29	7·6	52	
	3	6,200	30	3	29	
	4	6,345	31	7·6	60	
	5	6,310	31	3	38	

* Protein intake is expressed as g. per 100 ml. fluid intake, for the twenty-four hours preceding the estimation of the corresponding values of weight, haematocrit, blood and urine urea.

intravascular compartment has first priority, after which any water administered is proportionately shared between the extravascular compartments (increase in weight) and the kidneys for excretion purposes (fall in blood urea).

In the cases with an initial temporary rise of blood urea due to high protein intake the subsequent course was similar if the rehydration was uncomplicated and after restriction of the amount of protein given.

Eleven of the infants of this series died, and autopsy was performed on nine of them. Of these nine, five died after their dehydration was corrected and their blood urea had fallen to normal or near normal levels, and in none of these five was a renal lesion found at autopsy; two died of pneumonia, one of meningococcal meningitis, one of B. coli septicaemia, and one of congenital heart disease.

In the remaining four cases the primary illness was gastro-enteritis and all had had one or more relapses. The blood urea in the late stages of their illness rose still higher, even during temporary improvement of their hydration, after intravenous administration of fluids. A typical example is given in fig. 5, where it can be seen that the significant fall in haematocrit, indicating successful relief of dehydration, was accompanied by a marked rise in the urea of the blood. In all four cases a renal lesion, called dehydration nephrosis by some, was found at autopsy. This lesion consisted in degenerative and regenerative changes of the tubular epithelium with deposition of calcium salts.

It seems, therefore, that a continuously rising blood urea in spite of rehydration indicates the development of an organic renal lesion and that it carries a bad prognosis. The causes and mode of development of this organic lesion are not clear. All four infants were very ill, and in three of them the illness lasted more than twenty days. As other infants with the same degree of severity finally recovered, and as in one of these four patients the illness lasted for six days only, it seems as if severity and duration of the illness are not the only factors responsible for the organic renal lesion.

Discussion and Conclusions

The collected data may help in answering some of the following questions.

1. **Is this form of azotaemia extrarenal ?** Against the presence of an organic renal lesion are: (a) the absence of constant and significant urine findings, (b) the rapid fall of the blood urea in the majority of the cases after uncomplicated rehydration, and (c) the absence of kidney lesion in cases which shortly before death presented this form of azotaemia (five cases in the present series and similar cases of previous authors).

It has already been mentioned that in four cases of this series an organic renal lesion was found at autopsy; a similar though not identical histological picture has been reported in infants by Schloss (1918), Lightwood (1935), and Butler et al. (1936). How can these organic renal lesions be accounted for ? Gsell (1935) and Rohland (1936) suggested that the azotaemia in dehydration is at first always functional, but that if the dehydration lasts for a long time without being relieved irreversible changes may take place in the tubular epithelium. It has been suggested (Butler et. al., 1936) that this lesion is due to physicochemical changes which take place in dehydration, but the mode of development is not clear. It has been pointed out already that the duration and severity of symptoms are not the only factors responsible for the development of the renal lesion described.

2. **How does azotaemia develop in dehydration ?** There are two theoretical possibilities; increase in the amount of urea formed in the body, or interference with its excretion.

The first can play only a secondary role, because the amount of urea formed in the body as a result of dehydration (Black et al., 1943-44) is minute compared with the urea formed and excreted under normal conditions. The well known fact that in dehydration the urine volume is diminished strongly suggests that interference with the excretion of urea is the preponderant mechanism.

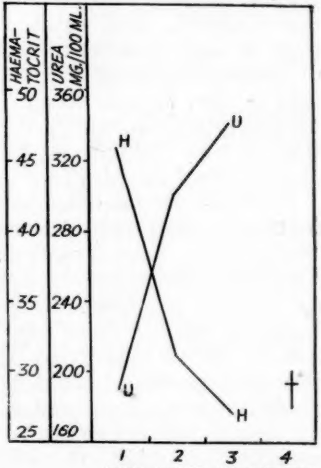

FIG. 5.—Changes in blood urea during rehydration (rise before death).

But how does dehydration interfere with the urea excretion ? A critical review of the work done and the theories advanced was made by Kerpel-Fronius

(1936) for extrarenal azotaemia in general, and by Black (1942) for extrarenal azotaemia following gastro-duodenal haemorrhage. Schoenthal et al. (1933) found a diminished urea clearance in dehydrated infants.

In order to find out if haemodynamic factors (reduction of blood volume, fall of blood pressure, increase in colloidosmotic pressure and blood viscosity) or general dehydration are more important the cases of the present series were divided into three groups: (A) cases in which plasma volume was reduced relatively more than total body water (predominance of haemodynamic factors); (B) cases in which total body water was reduced relatively more than plasma volume; and (C) cases in which intra- and extravascular compartments were equally dehydrated.

As can be seen from figs. 2 and 3, the dehydration was confined to one (extravascular) compartment in two infants only. From the other thirty-two cases for which sufficient data were available for such a classification, eleven belonged to group A, sixteen to group B, and seven to group C.

As each group contains a fair number of cases, and as dehydration confined to one compartment only is rare, it seems that interference with the excretion of urea is due in most cases of the present series to a combination of two groups of factors. The one group consists of haemodynamic factors, the importance of which was experimentally shown by Goemoeri et al. (1939). The other factor is general reduction of the total body water (tissue dehydration), as a result of which there is not enough water available for urine formation. It is of interest to notice that a slight rise of the blood urea within normal limits occurs in the first few days of life (McCance and Widdowson, 1947) and that this is thought to be due to a temporary physiological dehydration.

3. **What are the other factors, which with a given degree of dehydration determine the ultimate rise in blood urea ?** Such factors may be:

(a) The concentrating capacity of the kidney. As already mentioned there are great individual variations, and Young and McCance (1942) have clearly proved the great variability of the urea clearance in normal and dehydrated infants. When the urine volume is reduced as a result of dehydration, the infant whose kidneys have lower concentrating capacity, will, other things being equal, develop a higher blood-urea level.

(b) Infection. The increased tissue protein breakdown and consequently increased urea formation during infection is a well established fact. But in the present series infection acting in this way could not be held responsible for the azotaemia because (1) dehydration without infection as in cases of pyloric stenosis has caused blood urea levels as high as 190 mg., and (2) infection without dehydration in the control series has never been the cause of azotaemia. But infection may be indirectly responsible for azotaemia since it was often the cause of dehydration.

(c) Starvation. Here again the extra urea which may be formed as a result of increased protein breakdown is minute in comparison to the amount retained. Its insignificant role is well demonstrated by a quick fall in blood urea after rehydration on a water diet while the starvation still continues. If the excretion of urea is not, therefore, interfered with, any extra urea formed as a result of increased protein breakdown, either from infection or from starvation, can be easily eliminated through the kidneys.

(d) Protein intake. The influence of the protein intake on the blood urea level under abnormal and normal conditions has been demonstrated. It is of interest to notice that the best correspondence between protein intake and rise or fall in blood urea was obtained when the protein intake was expressed in relation to total fluid intake and not to body weight.

These results confirm Schiff's (1929) opinion on the importance of the protein intake in determining the water requirements of the body.

The high blood urea values in most cases in this series cannot be due to high protein intake alone, because the protein intake could not be very high before admission and because even very high protein intake (7·6 per cent. of total fluid intake) did not raise the urea to more than double the normal value if the hydration was normal. But, given a deficient excretion due to dehydration, it can very well be one of the most important factors determining the degree of azotaemia.

It is suggested that, dehydration being invariably present in extrarenal azotaemia, other factors determining the degree of azotaemia in each particular case are the concentrating capacity of the kidneys, the amount of protein intake, and, to a lesser degree, an increased tissue protein breakdown the causes of which are dehydration, starvation, and infection.

4. **Has the increased urea harmful effects in itself and can it influence the course of the illness?** Although an increased urea content of the body has been said to be harmful in various ways (Harrison and Mason, 1937), the existence of such harmful effects for the human body has not been clearly proved. Since in the present series azotaemia was always combined with dehydration and often also with infection, no conclusion could be drawn as to whether the increased urea was in itself harmful. But in a few cases there was a temporary hiatus between dehydration and azotaemia. These were the cases in which, because of high protein intake, the blood urea rose during rehydration. It seemed as if in some infants the increase in blood urea preceded a relapse in dehydration. A typical case is presented in fig. 6, where it can be seen that on the second day there was a rise in the blood urea due to a very high protein intake although the fall in haematocrit and the increase in weight showed a satisfactory progress of rehydration. The following day this progress had stopped, the weight had fallen, the haematocrit had risen again, and the infant was clinically more dehydrated. This relapse could not

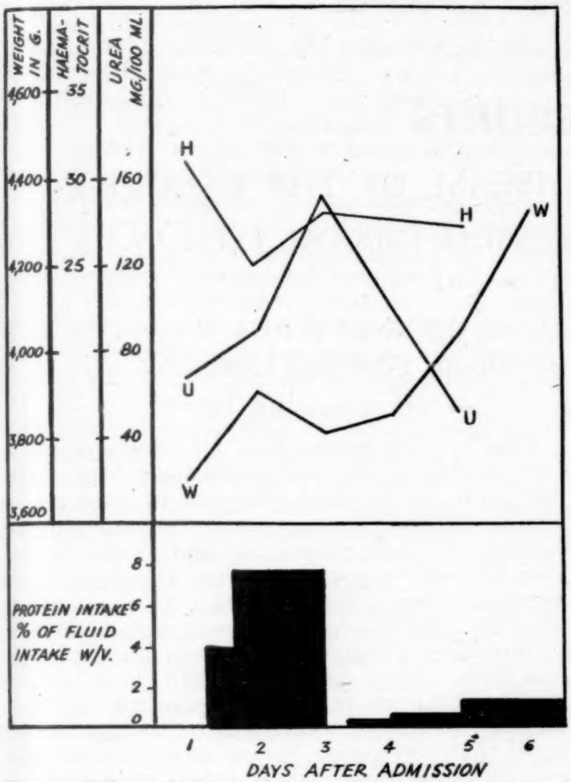

FIG. 6.—Effect of high protein intake on blood urea and on rehydration.

be accounted for by any change in the number or character of the stools or by any recurrence of vomiting. The high protein intake was discontinued and a quick recovery followed.

McCance and Young (1943-44) demonstrated that intravenous injection of urea caused an increase in the output of water, and that this happened to some extent even during dehydration. The above mentioned relapse in dehydration may have been caused by the same mechanism, though direct proof is not available. The practical implication of this observation is that the use of therapeutic feeds of a high protein content (more than 4 per cent. for young infants and more than 6 per cent. for older) may cause a relapse of the dehydration. The use of such feeds is therefore not justified, particularly because the same therapeutic effects can be obtained with feeds of a normal protein content.

5. **Is the estimation of the blood urea in dehydrated infants helpful ?** One estimation on admission simply indicates the presence and, roughly, the degree of dehydration. It is not, therefore, of any immediate practical value, as the presence of dehydration is easily detected on clinical examination and the degree may be more quickly and more directly estimated by other methods. Stransky (1920), on the basis of clinical observations, reached the same conclusion.

Successive estimations may be of greater help. A quick fall indicates a satisfactory rehydration and is of good prognostic significance as regards the dehydration. A continuous rising or persistence in high levels, in spite of fall in haematocrit, makes the prognosis poor because it may indicate the development of irreversible changes in the renal tubules.

Summary

1. A study was undertaken of forty-seven sick infants presenting blood urea values of from 50 to 500 mg. per 100 ml. of blood.

2. An attempt was made to define the nature of this azotaemia and the conditions under which it may develop.

3. This azotaemia is always extrarenal at the beginning, and the basic condition necessary for its development is dehydration due to a variety of causes.

4. Contributory factors which may determine the degree of azotaemia are the amount of protein intake, the concentrating capacity of the kidney, and to a lesser degree increased tissue protein breakdown due to infection or starvation.

5. Persistence of high blood urea values in spite of rehydration is of bad prognostic significance as it indicates the development of irreversible changes in the renal tubules.

I am much indebted to Professor J. C. Spence for drawing my attention to this problem and for his continuous advice and encouragement, to Dr. D. Gairdner for his help, advice, and criticism, and to Dr. D. Court for his valuable suggestions.

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CASE REPORTS

CONGENITAL FIBROCYSTIC DISEASE OF THE PANCREAS

A REPORT OF TWO PROVED CASES OF DISSIMILAR CLINICAL TYPES IN SIBLINGS

BY

AGNES R. MACGREGOR, M.D., F.R.C.P.Ed., and KENNETH RHANEY, M.B., Ch.B.
(From the Department of Child Life and Health, Edinburgh University)

In her important paper on cystic fibrosis of the pancreas, Andersen (1938) showed that this disease manifests itself as one of three clinical syndromes. This has been confirmed by many subsequent workers. The syndromes have the following salient features:

(1) Newly born infants who die within a week of birth from intestinal obstruction due to inspissation of meconium, sometimes associated with peritoneal bands, volvulus or atresia.

(2) Infants between one week and six months old, in whom the principal features are early failure to thrive, often despite a good appetite, large fatty stools, and intolerance to fat in the diet. These infants invariably present an intractable infection of the respiratory tract resembling whooping-cough, with paroxysms of coughing and cyanosis. This infection appears to be the immediate cause of death.

(3) Children over six months of age, who present the clinical features of the coeliac syndrome.

It is now recognized that congenital fibrocystic disease of the pancreas has a high familial incidence. In a recent paper on the genetics of the disease, Andersen and Hodges (1946) reviewed the literature and concluded that 'it occurs among siblings, twins and more distant relatives with a distribution which is compatible with the hypothesis that it is carried as a relatively infrequent hereditary trait.' They collected from the literature several instances in which one sibling suffered from congenital intestinal obstruction and another from proved pancreatic disease presenting one of the other clinical syndromes (Flax et al., 1942; Deem and McGeorge, 1941; Attwood and Sargent, 1942; Philipsborn et al., 1944). In none of these instances were both siblings examined at autopsy. The following case records illustrate the occurrence of dissimilar clinical types in siblings, one of whom suffered from congenital intestinal obstruction. Both were proved by post-mortem examination to have cystic fibrosis of the pancreas.

Case Reports

Case 1. The patient was a female infant aged four months at the time of admission to hospital. She was the second child of her parents, the first-born being a healthy girl of six years. She was admitted because of cough since birth, and stridor for two months. She was said to have been one month premature (birth weight 5½ to 6 lb., spontaneous delivery). She was well at birth, but attempts to institute breast feeding failed after three days. She was given boiled cows' milk, and later National Dried Milk, in appropriate amounts with the addition of adequate vitamins. The appetite was good until one week before admission, when it became capricious, and at some feeds only one ounce was taken.

She was said to have had a cough since birth, but this did not cause distress. Two months before admission she began to vomit after feeds, and developed stridor, which was accompanied by cyanosis during the last month. At that time she developed acute catarrh with nasal discharge. The cough became worse, with paroxysms. This was associated with great distress and cyanosis, and aphonia developed. During the last week before admission, the symptoms became more severe. Diarrhoea developed, 'frequent loose, brown stools' being passed. The appetite became poor and she began to lose weight.

CLINICAL EXAMINATION. The infant was well proportioned but of poor nutrition, her length being 22 inches, and her weight 8 lb. 13½ oz. The abdomen was not distended, and no enlargement of the liver or spleen could be detected. Muscle tone was poor, and great weakness resulted from the paroxysms of coughing. There was slight cyanosis. The alae nasi were moving. There was no nasal discharge. The fauces were slightly congested. The chest was held in the position of inspiration. The lower ribs were indrawn on inspiration. A resonant percussion note was obtained, and on auscultation the expiratory phase was prolonged.

No abnormality of the alimentary system was found. The nervous system was normal. The white blood count was 12,000 per c.mm. of blood, haemoglobin 75 per cent. (Sahli). The temperature was 98° F., the pulse 134 per minute, and respiration 36 per minute. X-ray examination on admission revealed 'no gross pulmonary lesion.' Three days before death a second examination showed 'exaggerated shadows at both bases, consistent with bronchiectasis.'

Further Progress. Death occurred after sixteen days in hospital. During this time she became progressively weaker and the respiratory difficulty more severe. Vomiting followed all feeds, and the stools became frequent, offensive, and watery. They were not noticeably fatty. During the whole period in hospital the temperature was normal or subnormal, except for two occasions when it rose to 99° F. Owing to the cyanosis, oxygen was administered continuously. Laryngoscopic examination revealed no obstruction in the larynx, which was inflamed. There was thick secretion in the pharynx. Six days before death she collapsed and was pale, cold, cyanosed, and gasping for breath. Penicillin was given by intramuscular injection until death, without obvious beneficial result.

Post-mortem Report. The body was that of a small, emaciated female infant. The chest was held in the position of inspiration, with the ribs elevated. There was no jaundice of the skin. The larynx, trachea, and main bronchi were filled with thick yellow pus, and the mucous membrane was slightly congested. There was no anatomical abnormality of the larynx.

The left pleural sac contained air under pressure, but the left lung was only partly collapsed. In both lobes there was interstitial emphysema, with large air bullae under the pleura and in the septa. The right pleural sac was healthy, and the right lung showed only vesicular emphysema. No consolidation could be detected in either lung. Throughout the whole bronchial system there was severe purulent bronchitis, all the bronchi down to the smallest visible twigs being filled with thick yellow pus. There was no obvious dilatation of the bronchi, and suppurative disorganization was not evident to the naked eye. The lymph nodes in the roots of the lungs were a little swollen and deep red.

The heart and pericardium were healthy. The alimentary tract showed nothing of note. The peritoneal sac was healthy. The liver was not enlarged but was bright yellowish brown, and showed a considerable amount of bile staining. The gall-bladder contained dark green bile, which was easily expressed into the duodenum. The spleen was of appropriate size and showed nothing of interest. The kidneys were rather paler than usual, but otherwise normal. The pancreas was rather below the expected size, of about normal consistence, but slightly nodular on the surface. It was not obviously fibrosed.

The head was not examined.

Bacteriological Report. The pus in the bronchi contained immense numbers of Gram-positive and Gram-negative bacilli, which, on culture, proved to be a diphtheroid bacillus and Bacillus lactis aerogenes. Staphylococcus aureus was not found in the direct film or on culture.

Microscopical Report. Pancreas (fig. 1, p. 59). The gland acini were formed of small, atrophied cells, and their slightly dilated lumina contained plugs of inspissated secretion. Similar material was present in the lumina of intralobular and interlobular ducts, which were slightly dilated. One of the larger ducts in the head of the pancreas was also dilated and its lumen obstructed by inspissated material. The islets of Langerhans were normal. In many parts there was a considerable increase of interlobular and interacinar fibrous tissue. The amount varied, and in those places where it was greatest there was a reduction in the number of acini.

Lung. The bronchi of all sizes were filled with mucus, among which were masses of bacteria and variable numbers of polymorph leucocytes and epithelial cells. The inflammatory cells were surprisingly scanty and much degenerated. Some bronchi showed a moderate amount of inflammatory cell infiltration of the wall, with both mononuclear cells and polymorph leucocytes. The epithelial lining was intact in the majority, but in some of the larger bronchi the ciliated epithelium had been replaced in parts of the wall by stratified squamous epithelium. Most of the mucous glands in the walls of the large bronchi were actively secreting, but others were lined with low cubical cells, and the lumina were dilated and contained inspissated secretion of a hyaline character, staining strongly with eosin (fig. 2, p. 59). There was no bronchiectasis and no disorganization of the bronchial walls. The inflammatory process had not extended to the alveoli. There was a moderate degree of vesicular emphysema.

Liver. There was severe fatty change, affecting principally the portal zones of the lobules. There was no increase in fibrous tissue and no abnormality of the bile ducts was noted.

Summary. This was a case of purulent bronchitis with cystic fibrosis of the pancreas and fatty change in the liver.

Case 2. The patient was a male infant born sixteen and a half months after the birth of his sister (case 1). His birth weight was 5 lb. 14 oz. Delivery was spontaneous, but the baby was limp and cyanosed at birth. During the first two days respirations were shallow and murmury, and he had several attacks of respiratory failure with cyanosis. Chest expansion was poor, and a few crepitations were heard. Meconium was said to have been passed on two occasions: once on the second day and once on the third day. No abnormality of the meconium was noted. Death took place on the third day.

Post-mortem Report. The body was that of a male infant weighing 5 lb. 14 oz. The umbilical cord was partly dried. There was slight jaundice.

When the abdomen was opened a greatly distended loop of bowel presented. It was approximately six inches long, and its lower end was four inches proximal to the ileo-caecal valve. It contained meconium, which was of normal colour but more viscid and cohesive than usual. Proximal to this loop no abnormality was noted in the bowel and its contents. At the distal end of the loop the character of the contents underwent a sudden change, and the remainder of the ileum contained a small quantity of pale green, thick, paste-like material, which could be forced along the bowel only with great difficulty. The ileo-caecal valve was patent. The caecum contained a little of the same material. The colon contained white mucus and was contracted. Obstruction was apparently present at the distal end of the dilated loop, but had produced no hypertrophy of the wall. There was no stricture, peritoneal band, atresia, or volvulus.

The pancreas was macroscopically normal. The liver was intensely congested. The biliary passages were healthy. Both kidneys contained heavy deposits of uric acid crystals.

The larynx, trachea and main bronchi contained a small quantity of frothy, blood-stained fluid. The pleural and pericardial sacs were healthy.

Both lungs showed widespread pneumonia, only a small strip at the anterior border of the right lower lobe being healthy. The remainder of both lungs was intensely congested and of greatly increased bulk and consistence. The right lung was more affected than the left. The cut surfaces were very moist, and turbid fluid was expressed from the bronchi.

The heart showed no developmental abnormality. Both atria were distended. The ventricles were contracted. The oesophagus was congested throughout its length. The thymus gland was healthy.

The venous sinuses of the dura mater, and the veins in the lepto-meninges, were congested. The brain substance was healthy.

BACTERIOLOGICAL REPORT. A culture from the lung yielded a growth of Bacillus coli and Staphylococcus albus.

MICROSCOPICAL REPORT. Pancreas (fig. 3, p. 59). Atrophy of the acinar tissue was revealed. In most of the lobules the acini were reduced in number and in size, being composed of small cubical or flattened cells. In many acini the lumen was slightly larger than normal and was filled with inspissated secretion of hyaline appearance. Some of the acinar cells contained apparently normal secretory granules, but in others there were large, faintly acidophil, hyaline bodies, which occupied much of the cytoplasm, and appeared to be of the same nature as the inspissated material in the lumen (fig. 4, p. 59). In contrast, some acini, lined by atrophied cells, showed no visible lumen. The small interlobular, and many intralobular, ducts were slightly dilated and filled with inspissated secretion. Some of the intralobular ducts were empty and not dilated. The larger pancreatic ducts were not present in the tissue available for examination. The islets of Langerhans were greatly reduced in number and size. There was a slight increase in interlobular and interacinar stroma, which was oedematous but showed no evidence of inflammation.

Lung. The lungs contained a large quantity of vernix, some of it in lumps, but most of it forming thick membranes lining the walls of terminal bronchioles and alveolar ducts. Proximal to it the respiratory passages were over-distended, but the distal parts were atelectatic and compressed. Widespread patchy exudate had developed in relation to the vernix and was composed mainly of polymorph leucocytes. Other areas were filled with blood and oedema fluid. There was no abnormality of the bronchial mucous glands.

The liver showed intense congestion, and in the portal zones some of the cells contained small globules of fat.

Oesophagus. There were no pathological features apart from intense congestion of the submucous coat.

The spleen showed nothing of interest.

Kidneys. The collecting tubules were dilated and contained the structureless debris found in association with deposits of uric acid crystals.

SUMMARY. This was a case of meconium ileus associated with cystic fibrosis of the pancreas. There was inhalation of the vernix, with pneumonia.

Comment

The occurrence of pancreatic lesions characteristic of congenital fibrocystic disease in these two siblings provides strong evidence in favour of the conclusion of Andersen and Hodges (1946) that meconium ileus in the newborn has the same etiology as the two clinical syndromes that reveal themselves in later infancy. It also confirms the conception that the clinical type of the disease is determined by the age at which the pathological process in the pancreas results in a severe deficiency of exocrine secretion. If this stage is reached at the time of birth, meconium ileus results; if in the early months of life, the respiratory type; if in later infancy, the coeliac type,

If the pathological changes are due, as is believed, to inspissation of secretion in the acini and ducts, and if the obstruction thus caused persists, the degree of atrophy, dilatation and fibrosis will depend, at least in part, upon the duration of life. Accordingly all these features were more fully developed in the pancreas of the older child, although at the time of her birth the pancreatic function was less impaired than in the case of the infant who developed meconium ileus.

Stenosis or atresia of the main pancreatic duct has been found in a proportion of cases of congenital fibrocystic disease (Kornblith and Otani, 1929; Hurwitt and Arnheim, 1942; Kauffmann and Chamberlain, 1943). Unfortunately the main pancreatic duct was not examined in either of the cases under discussion. In case 2 certain features were found that could not readily be explained by

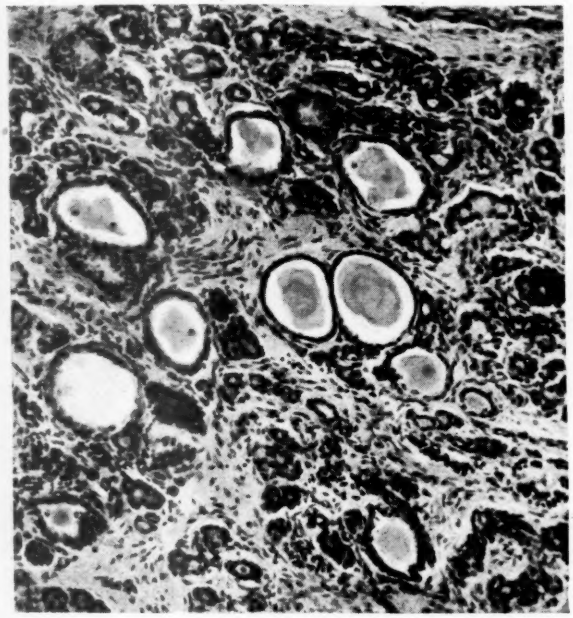

FIG. 1.—Case 1. Pancreas shows dilated acini and ducts containing inspissated secretion. Other acini are atrophied. Inter- and intra-lobular stroma is increased. H. and E. × 115.

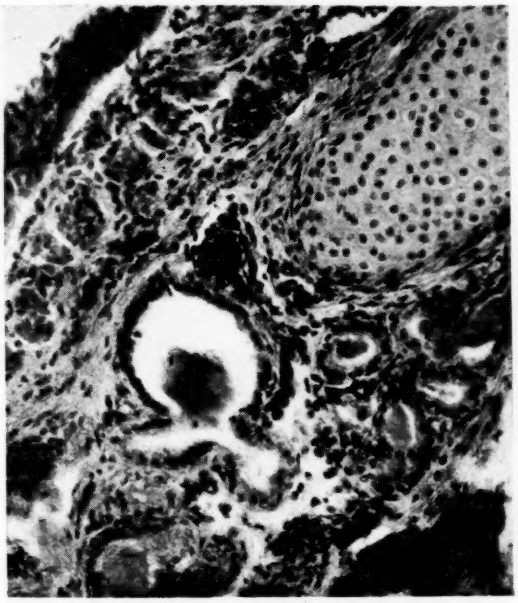

FIG. 2.—Case 1. The wall of the bronchus shows dilatation of mucous glands, with inspissation of secretion. H. and E. × 160.

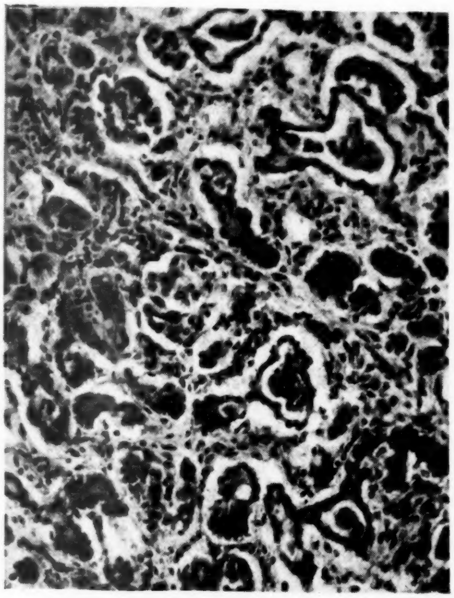

FIG. 3.—Case 2. The pancreas shows atrophy of acini. The ducts and some acini are dilated and contain inspissated secretion. The stroma is increased. H. and E. × 160.

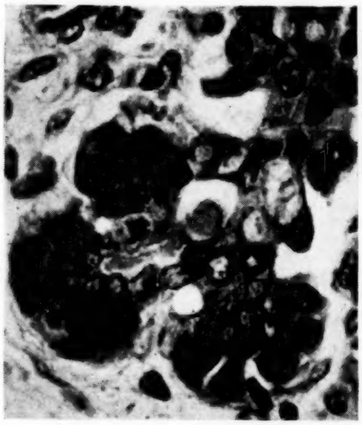

FIG. 4.—Case 2. Pancreas. Acinus showing hyaline bodies in the cells and inspissated secretion in the lumen. H. and E. × 650.

PLATE I

obstruction in the main duct, and suggested an abnormality of the acinar cells. Some of the intralobular ducts that showed no evidence of obstruction, being undilated and empty, were related to acini that contained inspissated secretion and were slightly dilated. Some acinar cells contained hyaline bodies similar to inspissated secretion in the lumen. This strongly suggests that they were producing an abnormal secretion.

In case 1, changes suggesting an abnormality of secretion were found in the mucous glands of the bronchi. Farber (1944b) has emphasized that the pancreas is not the only gland in which changes in the physical character of the secretion occur. To the involvement of the tracheal and bronchial mucous glands he attributes the accumulation of thick mucus in the respiratory passages, which causes the paroxysmal cough and respiratory obstruction.

It thus appears that the characteristic pathological changes of this disease are the result of an error of secretory function, and that other glands in addition to the pancreas may be affected. The names by which the condition has become commonly known, fibrocystic disease, or cystic fibrosis of the pancreas, are, therefore, unfortunate, for as May (1947) has observed, ' The pathology includes much more than fibrosis, but the name " cystic fibrosis " which has been proposed is definitely misleading. The dilated ducts and acini are not true cysts, and there actually is another rare condition in which there is an involvement of the pancreas with numerous true cysts.'

In most of the reported cases the organism responsible for the respiratory infection was Staphylococcus aureus. The character of the purulent bronchitis in case 1 was similar to that found in other cases of fibrocystic disease of the pancreas in which Staphylococcus aureus was the causative organism. This organism was not present in films and cultures made at autopsy: these yielded diphtheroid bacilli and Bacillus lactic aerogenes. The character of the pus and the microscopical appearance of the bronchi were in keeping with an infection of low virulence. It is possible that Staphylacoccus aureus had been present, and had been eliminated by penicillin therapy, but no bacteriological investigations of the bronchial secretions were made during life.

Summary

The occurrence of fibrocystic disease of the pancreas in siblings is reported. One died of respiratory infection at the age of four months, and the other with meconium ileus at the age of two days. In both cases the diagnosis was proved by autopsy.

The pathological changes in the pancreas appeared to result from an abnormal secretion of the acinar cells. A similar abnormality was present in the bronchial mucous glands of the infant that died of respiratory infection.

We wish to express our thanks to Prof. Charles McNeil, and Dr. W. F. T. Haultain for permission to publish the cases and for the use of the clinical records. We are also indebted to Dr. J. L. Henderson for clinical particulars of both cases and for helpful criticism. We are grateful to Prof. R. W. B. Ellis for his help and encouragement.

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CONGENITAL DEFECT OF THE SCALP: AN INFANT WITH A BULLOUS LESION AT BIRTH

BY

SIMON YUDKIN, PH.D., M.B., M.R.C.P., D.C.H.
Nuffield Fellow in Child Health. (From the Mothers' Hospital, London)

The following case seems worth recording because of the light it may throw on the etiology of this comparatively rare condition.

Case History

S. P. was born on April 28, 1947. She was the first child of normal parents. Pregnancy and labour were normal, and the birth weight was 7 lb. 13½ oz.

At birth there was a flaccid, oval, bullous swelling measuring 1⅛ in. by ⅝ in. over the anterior inferior end of the left parietal bone (Plate II). The wall of the swelling was translucent, purplish in colour, and devoid of hair and sweat glands. The thin wall arose directly from the surrounding skin, which was quite normal: a small amount of serous fluid was oozing from a tiny puckered area in the wall. The floor of the lesion consisted of the parietal bone, and there was no evidence of communication between the lesion and the cranial cavity. About half an inch in front of this main lesion was a small area ¼ in. in diameter where the skin appendages were absent but the scalp was of normal thickness. There were two tiny similar areas at the posterior end of the main lesion. A radiograph of the skull showed no bony defect.

The child was otherwise quite well and there were no other congenital abnormalities. The mother's Wassermann reaction was negative; there was no consanguinity of the parents, and no history of any similar condition in any member of the family.

The oozing stopped after two days and the bulla became slightly more tense. When the child was seen at the age of four months most of the fluid had been absorbed and the wall was thickened. The small lesions were unchanged.

Comment

Of congenital defects of the skin, by far the largest proportion occur in the scalp. (Anderson and Novy, 1942). They have been variously attributed to trauma, amniotic adhesions, or developmental defect. The usual appearance at birth varies from a punched out, granulating ulcer to a thin cicatrix with no skin appendages (Abt, 1917). The appearance seen in the present case has not so far been recorded in an infant at birth although Ingalls in 1933 described five embryos of from 15 to 187 mm. in length, each with a bleb or bullous area in the dorsal midline of the head. Ingalls pointed out that the scalp is a region of marked embryological activity and that the presence of occasional faults in development was therefore not surprising. He suggested that the thin covering of the lesions he described might easily ulcerate and would account for the usual appearance at birth. In spite of the position of the lesion here described it seems likely that it represents a condition such as that described by Ingalls, although, however, it remained unbroken throughout pregnancy and the birth process.

Apart from the light thrown on the etiology of congenital defects of the scalp by this case there are other features of these defects that favour a developmental origin.

1. Amniotic adhesions are practically never found, and when present cannot always be related to the site of the defect (see Greig, 1931 for details).
2. Congenital defects of the scalp are usually in the midline, and if not, are usually symmetrical.
3. The history of birth trauma is usually very vague and could not account for the presence of healed or healing lesions at birth.
4. They are frequently multiple (Yudkin, 1947).
5. The whole thickness of the scalp and sometimes the underlying bone are affected.
6. Other developmental defects are fairly frequently present (Greig, 1931; Anderson and Novy, 1942). These include hydrocephalus, cranial meningocele, harelip, and posterior rachischisis.
7. The condition has occasionally occurred in more than one member of a family (Campbell, 1826; Mackay, personal communication).

I should like to thank Dr. H. M. M. Mackay for permission to publish this case.

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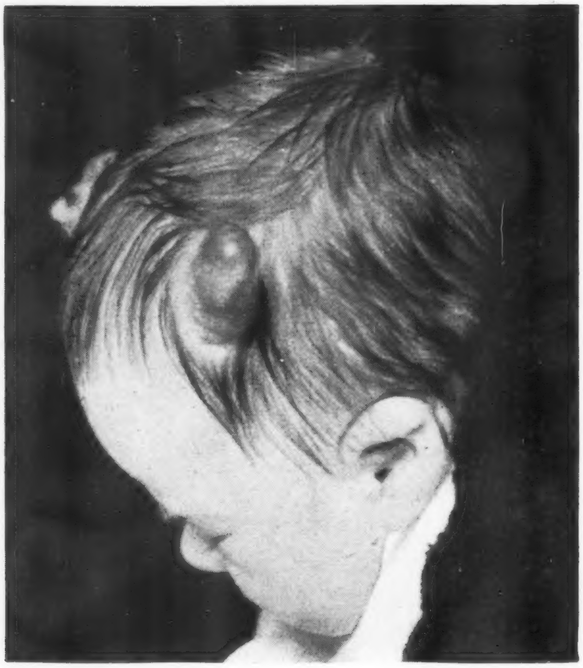
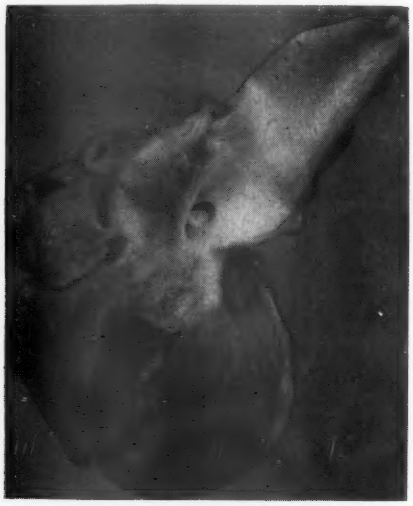
CONGENITAL DEFECT OF THE SCALP BY SIMON YUDKIN



Infant, showing bullous lesion.

CONGENITAL INTERRUPTION OF THE AORTIC ARCH BY MARGARET SEWART



Photograph of the mounted specimen.

PLATE II

CONGENITAL INTERRUPTION OF THE AORTIC ARCH

BY

MARGARET SEWART, B.Sc., M.B., B.Ch., D.C.H.
Late House Physician, Premature Baby Unit, Sorrento Maternity Home, Birmingham

The following case appears to be of sufficient rarity to warrant recording.

Mrs. B., aged 41 years, was delivered of her third child at home at 8 a.m. on July 23, 1946. The two previous pregnancies, in 1937 and 1940, had terminated normally at full term. Maternal health in this pregnancy was good. Delivery was by the vertex. The baby was in a state of blue asphyxia at birth, but responded well to resuscitation. Immediately after delivery the child was transferred to the City of Birmingham Premature Baby Ward, Sorrento Maternity Home, under the care of Dr. V. Mary Crosse.

Clinical findings. Examination on admission on July 23, 1946, showed a female premature baby of thirty-four weeks' gestation. Birth weight was 3 lb. 12 oz. The length (vertex to sole) was 17 in. The colour of the skin was good. Nothing abnormal was noticed in the cardiovascular system, but there was poor air entry over the left lung-field suggesting an area of atelectasis. Next day (July 24, 1946) the baby's condition was good enough to warrant the exposure necessary for a more detailed examination. This revealed a well baby with slight generalized oedema but no cyanosis. The veins over the backs of the hands were engorged. The feet were warm. The chest was broad and shortened from above downwards. The apex-beat was visible and palpable in its normal situation. There was marked visible and palpable pulsation in the left infraclavicular (pulmonary) area. There were no murmurs but the heart sounds at the pulmonary area were abnormally loud. All other systems were normal.

A diagnosis of congenital heart disease was made on these clinical findings. At 6 p.m. that evening the rectal temperature was 101·4° F. The baby became dyspnoeic, and there was poor air entry with fine crepitations over the left lung. As these findings suggested an aspirative pneumonia in an atelectatic lung, penicillin therapy (2,500 units intramuscularly three-hourly) was instituted. During the night of July 24-25 the breathing became increasingly laboured and the pulse more rapid and forcible, until each beat could be seen through the covering blanket. The child became cyanosed and died at 7.50 a.m. on July 25, 1946, aged 45 hours 50 minutes.

Post-mortem examination. This was made on July 25, 1946, by Dr. E. C. Allibone (Birmingham Children's Hospital). The body was that of a cyanosed baby in rigor mortis. The pericardium contained a small quantity of clear yellow fluid. The heart was normal in size. The right auricle was normal. There was a patency of the pars membranacea of the interventricular septum 4 or 5 mm. in diameter. The first part of the pulmonary artery was normal in position and direction, and, after giving off the right and left pulmonary branches, it was continuous, without change in diameter, with an artery which in position and appearance corresponded exactly with the descending part of the thoracic aorta. The left auricle and ventricle were normal. The ascending aorta and the arch of the aorta, after giving off the innominate artery and left common carotid, terminated in the left subclavian artery. There was no communication, nor a connexion by a fibrous band, between the aortic arch and the descending thoracic aorta (fig. 1 and Plate II).

The pleurae and lungs were normal. The peritoneum contained a few ounces of clear yellow fluid. All other organs, except for a few small tentorial tears, and two lacunae in the left parietal region of the skull, were normal.

Embryology

In order to understand the nature of this deformity it is necessary to refer to the branchial aortic arches of embryonic life. The forerunners of the greater vessels consist of six aortic arches on each side. The first, second, and fifth arches on each side disappear (indicated in fig. 2 by interrupted lines). The third aortic arches persist as the common carotid arteries. The fourth right arch forms part of the right subclavian artery. The fourth left arch forms that part of the arch of the aorta between the origin of the left common carotid and the entrance of the ductus arteriosus. The dorsal part of the last right arch disappears, its ventral part forming the right pulmonary artery. The dorsal part of the last left arch remains as the ductus arteriosus, the ventral part forming the left pulmonary artery. In the neonatal period the ductus arteriosus closes and is represented in the adult by the ligamentum arteriosum. The part of the left dorsal aorta between the fourth left aortic arch and the last left arch persists as the descending part of the arch of the aorta.

Discussion

In the case of Baby B. it will be seen from the above embryological note that the main defect lies

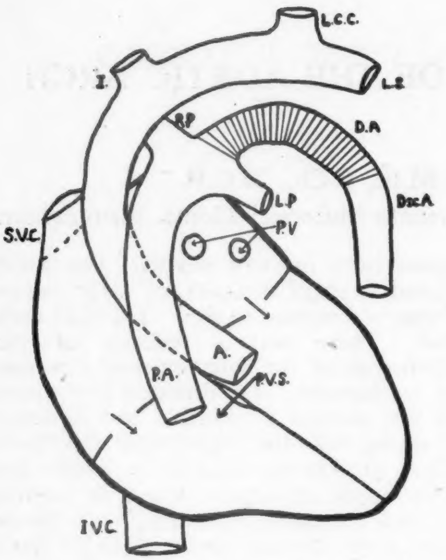


Fig. 1.—Diagrammatic representation of the abnormality

A. = aorta
Dsc. A. = descending thoracic aorta
D.A. = patent ductus arteriosus
I.V.C. = inferior vena cava
I. = innominate artery
L.C.C. = left common carotid
L.P. = left pulmonary artery
L.S. = left subclavian artery
P.A. = pulmonary artery
P.V.S. = patency of interventricular septum
R.P. = right pulmonary artery
S.V.C. = superior vena cava
P.V. = entrance of pulmonary veins

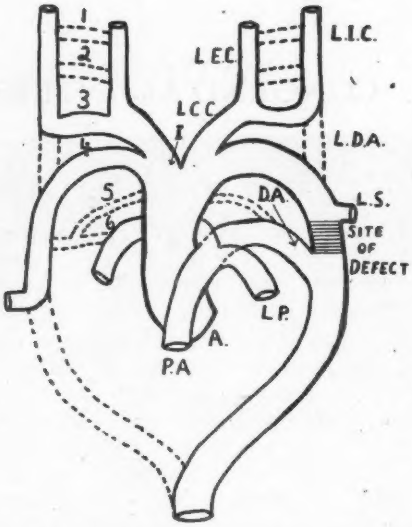


Fig. 2.—Diagrammatic representation of the aortic arches in man. The lettering has the same significance as in fig. 1, with the following additions.

L.D.A. = left dorsal aorta
L.E.C. = left external carotid
L.I.C. = left internal carotid

(The position of the left subclavian artery is placed as in post-embryonic life after rostral migration has taken place.)

in the abnormal disappearance of the distal part of the fourth left aortic arch, and of the left dorsal aorta between the fourth and the last left aortic arches. The fourth left aortic arch is here continued as the left subclavian artery. This defect leads to an interruption in the arch of the aorta, the descending part of the arch being absent. The descending thoracic aorta becomes thus a continuation of the patent ductus arteriosus (dorsal part of last left aortic arch). This condition is really an exaggeration of the infantile form of coarctation of the aorta, the part of the vascular system which is stenosed in the latter condition being completely absent in the present case. Because of this arrangement, there is a failure of direct communication between the arch of the aorta and the descending aorta, and the whole of the blood supply to the lower half of the body consists of blood from the pulmonary artery, via the patent ductus, which, in post-embryonic life should be unoxygenated. The baby ought, therefore, to have been cyanosed in the lower half and of good colour in the upper. The only explanation for the absence of this finding appears to lie in the presence of the patent interventricular septum allowing oxygenated blood to pass from the left side of the heart to the right in sufficient quantity to obscure this phenomenon.

The condition appears to be incompatible with any longer duration of life. Most reported cases died early in infancy, but one case lived to five and a half years (Maude Abbot, 1927).

There are six reported cases similar to that of Baby B. Maude Abbot (1927) collected five cases. William Evans (1933) describes one case (case 22). In none was the interventricular septum reported as having been patent.

Summary

A case of congenital interruption of the aortic arch is recorded. A short note on the embryology with reference to the pathogenesis of the condition is given. Reference is made to six reported cases.

I am indebted to Dr. V. Mary Crosse, Chief Medical Officer in Administrative Charge of City of Birmingham Maternity Homes and Premature Baby Unit, for permission to publish this case. I should also like to thank Dr. E. C. Allibone and Dr. H. S. Baar for their great help in reading and criticizing this paper, and for obtaining the photograph of the specimen.

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NEONATAL ARTHRITIS DUE TO PROTEUS VULGARIS

BY

ANDREW BOGDANOVITCH, M.B., D.C.H.
(From the Hospital for Sick Children, Great Ormond Street, London)

The main feature of this case is a bilateral purulent sterno-clavicular arthritis, which was secondary to umbilical infection. The case is described in view of the rarity of Proteus vulgaris infections of this type. The umbilicus is a frequent site of entrance of pyogenic infection in the neonatal period, and the full development of such an infection may manifest itself in many ways, including jaundice, meningitis, septicaemia, etc. Proteus vulgaris is normally found in decomposing organic matter of animal origin, such as sewage. It is also found in human faeces when normal intestinal mechanism is deranged, and Neter (1945) even found that 40 per cent. of normal infants under the age of one year, with no history of diarrhoea or similar disturbance, had this organism cultured from their rectal swabs.

It is of interest to note that Topley and Wilson (1946) give Proteus vulgaris as the fourth commonest organism to wound infection. Staphylococcus aureus, Streptococcus pyogenes, and Bacillus coli preceded Proteus vulgaris in that order. The umbilicus of a newly-born infant is liable to similar infection. Proteus vulgaris, when pathogenic, is responsible for inflammatory lesions such as cystitis. It also may give rise to abscess formation.

Case History

The patient, the second child of a healthy mother, was a girl born on June 29, 1946, one week prematurely, with a birth weight of 7 lb. 9 oz. The delivery was normal and spontaneous, requiring no instruments, but the infant was noticed to be cyanosed, and had to be given oxygen and coramine for the first two days of life. There was gradual improvement until the fourth day, when she became jaundiced and developed a temperature of 102° F. Examination of the urine revealed a Bacillus coli infection, which was treated with sulphathiazole and alkalis. A total of 3·25 gr. of sulphathiazole was given over four days.

On July 10 the infant was noticed to have swellings over both sterno-clavicular joints, and the urine still remaining infected; the sulphathiazole was replaced by sulphadiazine. On the following day the swellings were aspirated, and pus was withdrawn from the right sterno-clavicular joint, the fluid from the left joint being quite clear. Penicillin was commenced orally, 3,000 units being given every three hours. A catheter specimen of urine still revealed the presence of Bacillus coli in pure culture.

At this point the child was admitted to the Hospital for Sick Children, Great Ormond Street, London. The general condition was good. The infant was well hydrated, the mouth clean, and the eardrums were normal, but both sterno-clavicular joints were still greatly distended, and there was some discharge from the umbilicus, with a temperature of 101° F. The liver and spleen were not palpable. There was no oedema.

Investigations. Fluid from the right sterno-clavicular joint was purulent, from the left clear, and yellowish in colour. Each gave a pure growth of Proteus vulgaris. Blood culture showed no growth. The blood count was as follows: Hb 110 per cent.; red blood cells 5·1 million per c.mm. of blood; white blood cells 19,200 per c.mm., with polymorphs 68 per cent. and lymphocytes 32 per cent.

An umbilical swab yielded a pure culture of Proteus vulgaris, and a nasal swab was Staphylococcus aureus coagulase-positive. A post-nasal swab revealed Bacillus subtilis and Staphyloccus albus. No pathogens were isolated from a rectal swab.

A radiograph of the chest and sterno-clavicular joints showed no abnormality.

Progress and Treatment. Penicillin was continued, but, instead of orally, 1,500 units were given three-hourly by intramuscular injections. In addition, soon after admission (July 13, 1946), 1,000 units of penicillin were instilled into each sterno-clavicular joint after aspiration. On the next day (July 14) the umbilicus was already becoming cleaner, but it was decided to reinforce the penicillin with sulphadiazine in 0·25 g. doses six-hourly. The temperature had now become normal, and the swelling of the joints had diminished. The child was taking the breast well and was gaining weight.

On July 15 discharge from the umbilicus had ceased, but pus was again aspirated from the left sterno-clavicular joint and 1,000 units of penicillin were again instilled. Two days later the left joint was again aspirated and 1,000 units of penicillin instilled.

The Proteus vulgaris isolated in culture was found to be sensitive only to a concentration of 40 units of penicillin per 100 ml., a concentration which could only be achieved by local administration.

Systemic penicillin was accordingly discontinued, but the next day the temperature rose to 99° F., and it was therefore recommenced. The joint swellings had become less, the left more so than the right, and on July 23 penicillin was discontinued. A total of 106,000 units of penicillin had been given intramuscularly over fourteen days, with 1,000 units into the right joint, and 3,000 units in all into the left joint, thus making a grand total of 110,000 units.

The administration of sulphadiazine was stopped two days later (July 25), the total dosage being 11·75 g.

On discharge (July 28) the umbilicus was quite clean, and only slight swelling of both sterno-clavicular joints remained. The leucocyte count had fallen to 15,100 per c.mm. per cent. blood, with 41 per cent. polymorphs. Whilst in hospital the child, who had never appeared very ill, had made a steady gain in weight of 1 lb. 5 oz. during the 18 days.

When the child was seen a month after discharge, the left sterno-clavicular joint showed some deformity, and a radiograph revealed rarefaction of the inner end of the left clavicle with some derangement of the left sterno-clavicular joint. Apart from this the general condition of the child was excellent.

The child was next seen when it was nine months old. Her weight was 19 lb. 10 oz., and she looked extremely well. There was no apparent deformity of either sterno-clavicular joint, and movement at both joints seemed satisfactory. A radiograph, however, revealed that both joints were probably dislocated, and there was some consolidated widening at the inner ends of both clavicles. There was no evidence of bony destruction.

Conclusion

From this case it appears that Bacillus proteus infections in infancy, especially if localized, may be treated with full doses of sulphadiazine and penicillin with some hope of success. The non-irritability of the latter makes it suitable for local administration in high dosage. This in itself is probably as important as the rest of the treatment.

Summary

A case of Proteus vulgaris infection of both sterno-clavicular joints has been described.

The infection appeared secondary to that of the umbilicus.

Such cases are rare and usually fatal. The successful use of sulphadiazine with local and systemic penicillin is described.

I am indebted to Dr. Bernard Schlesinger for his help and permission to publish this case, to Dr. I. A. B. Cathie for advice on the bacteriological aspect, and to Dr. G. M. Donaldson for assistance on the ward.

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REVIEWS

The Child's Lung : Developmental Anatomy, Physiology and Pathology. By Stefan Engel, M.D., Formerly Associate Professor of Pediatrics, Medical Academy in Düsseldorf ; Special Research Fellow, The Hospital for Sick Children, Great Ormond Street, London. 1947. London: Edward Arnold and Co. Pp. 330. (Price 40*s*.)

In his preface, the author stresses his approach to the clinical aspects of pulmonary disease in childhood through morphological study of the respiratory system, and the need for three-dimensional methods in appreciating bronchial and lung structure. Much work has already been done along these lines, and unfortunately Part I of this book (which deals with the bronchial tree and bronchial glands) loses much of its value since most of the specimens from which the author obtained his data were Wood's metal casts, which lead to distortion of the bronchi. The best section in this part is that dealing with the bronchiolar wall. Chapter 18 ('The Elements of the Lung-Tissue ') gives a fair representation of the views held today, with perhaps the exception of the author's criticisms of Baltisberger on p. 229. It is curious that, whilst many people have failed to confirm Baltisberger's findings, there are some who have succeeded in demonstrating in normal healthy animal lungs, chiefly dog, muscle network around the alveolar duct. It is possible that there is a species difference, and also a particular technique necessary for their demonstration. Chapter 19 (' The Blood Supply of the Lung-Tissue ') consists of one page only, and does not even mention the bronchial vascular system, which supplies all the lung tissues with the exception of the portion of the respiratory tree distal to the respiratory bronchioles.

Whilst there is clearly a place for an authoritative work on the field with which the author has dealt, it must be admitted that this particular volume is not entirely adequate. The present high cost of book production perhaps tends to sharpen criticism of the matter published, but where certain aspects of the subject (for example the pathology included in Part I) have been equally well dealt with by other authors, it is felt that the presentation could be improved in subsequent editions, and a number of sections usefully expanded or clarified.

The Foundations of Health in Childhood. By NORMAN B. CAPON, M.D., F.R.C.P., Professor of Child Health in the University of Liverpool. The Convocation Lecture, 1947, of the National Children's Home. 1947. London. Pp. 76. (Price 2*s.* 6*d.*)

In lecturing to a lay audience, Professor Capon has been wise in getting back to facts and avoiding unsupported theory concerning the health of the individual child. Whilst much of his material will necessarily be familiar to paediatricians, his presentation is fresh and stimulating, and the whole book can be read with profit and interest. Indeed, it is surprising how much he has managed to compress into small compass without overburdening his pages with statistics. Where these are used, for example, in emphasizing the increasing importance of street accidents as a cause of death in childhood, they are used clearly and effectively. His final discussion on the attainment of optimum health is excellent.

Paediatrics for Nurses. By ARTHUR G. WATKINS, M.D., F.R.C.P., Physician in Children's Diseases, Cardiff Royal Infirmary; Lecturer in Paediatrics, Welsh National School of Medicine. Illustrated. 1947. Bristol: John Wright and Sons; London: Simpkin Marshall (1941), Ltd. Pp. 192. (Price 10*s.*)

The training of nurses in the care of the sick child is of such outstanding importance that every part of it deserves to come under critical scrutiny. Before writing a textbook for nurses' use, the paediatrician will naturally ask himself what he would like the fully trained nurse to know, and not solely what is included in her syllabus. He will realize that with the limited time which can be devoted to theoretical work, essentials must be emphasized and non-essentials reduced to a minimum or omitted altogether. He may well remember being asked to cover the whole field of paediatrics in two lectures to nurses undergoing their general training. Dr. Watkins' book will, therefore, be read with interest by those in any way concerned with the teaching of nurses.

What the author has, in fact, produced is a short, readable little book dealing with disease in childhood along orthodox lines. This in itself is no mean achievement, since the book is written clearly and concisely throughout, but it is something of a disappointment to find so little attention paid to the practical problems with which the nurse is likely to be faced or to the behaviour of the child when sick. Whilst the nurse must obviously know something of the diseases with which she will come in contact, there seems little object in training her to be a somewhat inferior doctor.

More information might usefully have been given about paediatric procedures in which she may be required to assist, about the diet and appetite of the sick child, his convalescence and rehabilitation, and the effects of homesickness on the child in hospital, and less about the Rhesus factor and haemoglobin levels. It is doubtful how much it will benefit the nurse to be taught that the serum calcium is reduced in rickets (even if this were generally true), but much heart-burning might be saved if it were pointed out that when collecting urine from a male infant the test-tube should not be placed in the erect position. Whilst the book is good of its kind, and is likely to be widely read, it is less certain that the kind is really that most suitable for nurses.

The 1947 Year Book of Pediatrics. Edited by ISAAC A. ABT, D.Sc., M.D., Emeritus Professor of Pediatrics, Northwestern University Medical School; with the collaboration of Arthur F. Abt, M.D., Associate Professor of Pediatrics, Northwestern University Medical School, 1947. Chicago: The Year Book Publishers Inc. Pp. 454. (Price 21*s.*)

This volume is dedicated by the publishers to Dr. Isaac Abt, on the occasion of his eightieth birthday. It is prefaced by appreciations written by Drs. Julius Hess, A. A. Weech, and E. F. Ellis, and it is appropriate that a year book which Dr. Abt has himself edited for forty-six years should serve as his Festschrift. Congratulations on a life of remarkable achievement will be extended to Dr. Abt by paediatricians throughout the world.

Developmental Diagnosis. Normal and Abnormal Child Development. By A. GESELL, M.D., and C. S. AMATRUDA, M.D. Second Edition: Revised and Enlarged. 1947. London: Hamish Hamilton Medical Books. Pp. 496. (Price 32*s.* 6*d.*)

Approximately seventy illustrative case histories have been added, and a section based on the authors 'Embryology of Behaviour' included. The last chapter, which is also new, deals with developmental paediatrics.

Infant Nutrition. A Testbook of Infant Feeding for Students and Practitioners of Medicine. By P. C. Jeans, A.B., M.D., Professor of Pediatrics, College of Medicine, State University of Iowa; and W. K. Marriott, B.S., M.D., late Professor of Pediatrics, Washington University School of Medicine. Fourth Edition. 1947. London: Henry Kimpton. Pp. 516. (Price 32*s.* 6*d.*)

A new edition of this well-known work is welcome, since there have been many advances in the science of nutrition since the last was published. Opportunity has been taken for complete revision of the text, and a number of illustrations have been added. Approximately half the book is devoted to the physiology of infant nutrition and normal feeding, and the remainder to disorders of nutrition and their treatment. The absence of references may be regretted, but in every other respect the book will be found most valuable.

Psychiatric Examination of the School Child. By M. BARTON HALL, M.D., Joint Honorary Medical Director, Liverpool Psychiatric Clinic. 1947. London: Edward Arnold and Co. Pp. 368. (Price 15*s.*)

This is a comprehensive and clearly written account of the diagnostic work of a child psychiatric clinic, the type and classification of cases referred for consultation, and the methods employed in history taking, examination, and the framing of records and reports. It is one of the most practical contributions to the subject that has been produced in this country.

Gardiner's Handbook of Skin Diseases. Revised by J. KINNEAR, O.B.E., T.D., M.D., F.R.C.P.Ed., D.L., Lecturer in Diseases of the Skin, St. Andrews University. Fifth Edition. 1948. Edinburgh: E. and S. Livingstone. Pp. 250. (Price 15*s.*)

Essentials of Fevers. By GERALD E. BREEN, M.D., B.Ch., D.P.H. Second Edition. 1948. Edinburgh: E. and S. Livingstone. Pp. 351. (Price 15*s.*)

Diseases of the Ear, Nose, and Throat. By I. SIMSON HALL, M.B., Ch.B., F.R.C.S.Ed., Surgeon to the Royal Infirmary, Edinburgh (Department for Diseases of Nose, Throat, and Ear). Fourth Edition. 1948. Edinburgh: E. and S. Livingstone. Pp. 463. (Price 15*s.*)

The above three books are well-known handbooks which are now brought up to date in new editions. All are well illustrated, including coloured plates, and the publishers are to be congratulated on maintaining a high standard of book production at what must nowadays be considered a very reasonable price.

Studies of the Free Art Expression of Behaviour Problem Children and Adolescents as a means of Diagnosis and Therapy. By M. NAUMBURG, Department of Clinical Psychiatry, New York State Psychiatric Institute and Hospital. New York, Nervous and Mental Disease Monographs, No. 71. 1947. Coolidge Foundation. Pp. 225. (Price $5.50).

Detailed case histories are illustrated by patients' drawings, and their interpretation.

Fundamentals of Immunology. By WILLIAM C. BOYD, Ph.D., Associate Professor of Biochemistry, Boston University School of Medicine. Second Edition, completely revised and rewritten. 1947. New York and London: Interscience Publishers. Pp. 519. (Price 36*s.*)

This is a standard work and the second edition has been brought fully up to date. It is more suitable for the research worker than for the practising clinician.

Aids to the Diagnosis and Treatment of Diseases of Children. By F. M. B. ALLEN, M.D., F.R.C.P., Lecturer in Infant Hygiene and Diseases of Children, Queen's University, Belfast. Eighth Edition. 1947. London: Baillière, Tindall and Cox. Pp. 268. (Price 6*s.*)

Fully revised since publication of the seventh edition in 1936, this book is likely to remain a popular member of the Aids series.

The Nursing of Tuberculosis. By O. V. BUXTON, S.R.N., and P. M. MACULLOCH, S.R.M.N. With a foreword by R. R. TRAIL, M.C., M.D., F.R.C.P. 1947. Bristol: John Wright and Sons. Pp. 124. (Price 7*s.* 6*d.*)

In spite of its title, the emphasis in this little book appears to be more on tuberculosis than on nursing. It is regrettable that so little attention has been paid to the tuberculous child, and such statements as 'Tuberculin skin tests . . . are of value only in a "negative" way' are typical. Since, however, much of the material is well presented, it is hoped these deficiencies may be made good.

The Medical Annual 1947. A Year Book of Treatment and Practitioner's Index. Sixty-fifth year. Edited by Sir HENRY TIDY, K.B.E., M.D., F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. 1947. Bristol: John Wright and Sons. Pp. 464. (Price 25*s.*)

Paediatrics is represented by contributions by Prof. C. McNeil, Dr. Reginald Miller, and the late Sir John Fraser, Dr. C. Swan writes on rubella and congenital malformations, Dr. Percy Stocks on vital statistics, and Dr. H. S. Banks on acute infectious diseases. The usual high standard is maintained.

Mothercraft in Pictures. Compiled by M. MASLEN JONES, S.R.N., S.C.M., M.T.S., Nursing Director Mothercraft Training Society, Cromwell House. 1947. London: Faber and Faber, Ltd. Pp. 66. (Price 7*s.* 6*d.*)

Sixty-six photographs, most of them excellent, are supplemented by short verbal instructions, and the book should be valuable for teaching purposes.